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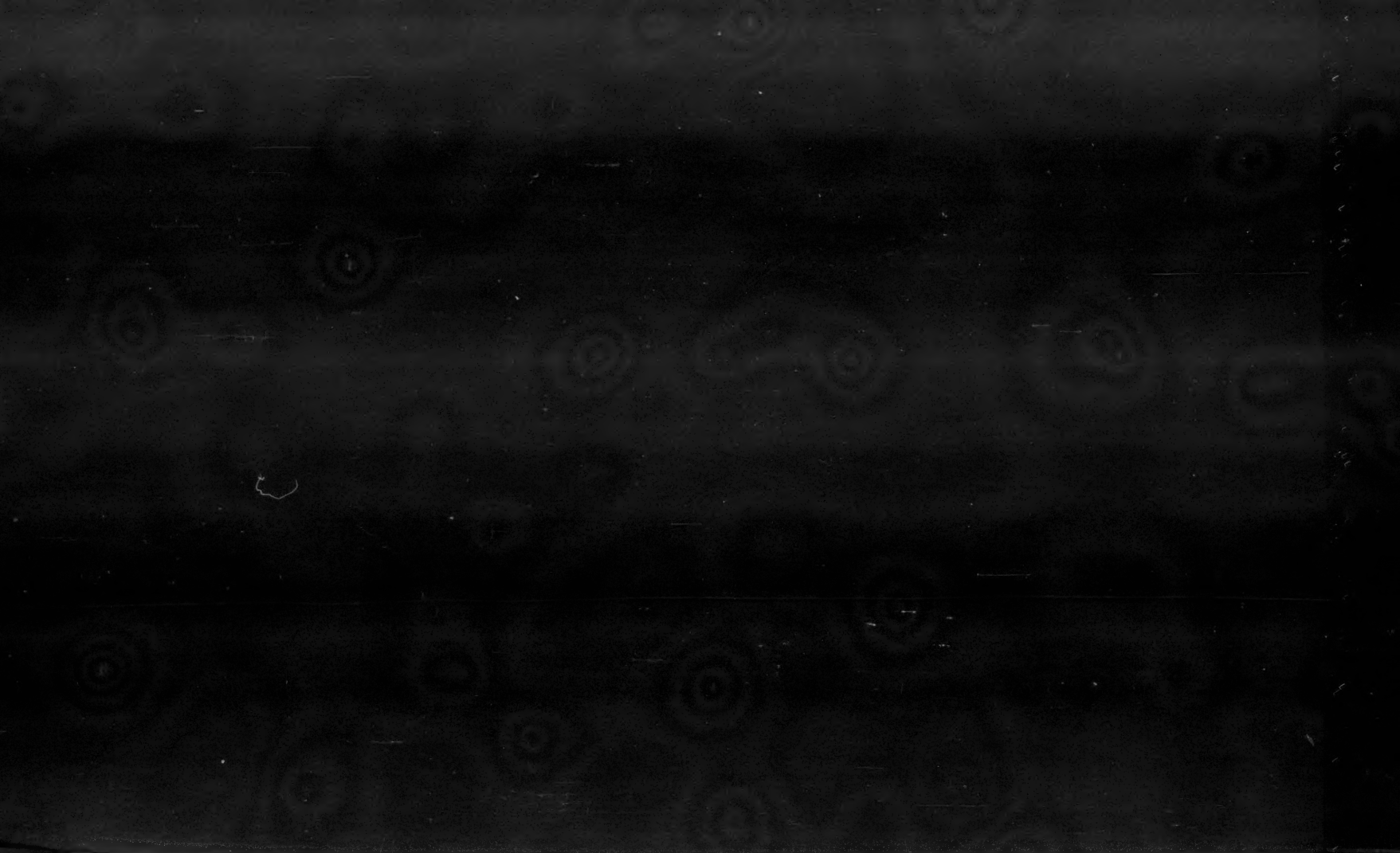


Acta Pædiatrica **43**: 399—410. Sept. 1954

A New Theory Concerning the Mechanism of the Initiation of Respiration in the Newborn

A Preliminary Report

by S. JÄYKKÄ

The opinion of the present time, regarding the expansion of the lungs is, in short, as SUNDAL expresses it: "At birth the lungs are airless but under normal conditions and with clear respiratory passages and normal respiratory movements, they gradually expand completely and symmetrically in a few days." The phenomenon would thus appear to be an inflation, and causes by inflowing air expanding of the alveoli by its pressure. If respiratory movements occur in the uterus, amniotic fluid instead of air should enter the alveoli. The question, of course, arises, whether fetal respiratory movements do take place in the uterus. The matter has been much discussed and a great amount of research work done, evidence being adduced both for and against the occurrence of fetal respiratory movements in utero. The prevailing opinion (PARMELEE) seems, however, to be that, from research work done on animal and human fetuses (SNYDER and ROSENFELD), it is practically certain that regular fetal respiratory movements do occur in utero. If this opinion is correct, one can neither understand nor explain, why the amniotic fluid has no expansive effect normally.

It is just as difficult to understand what expansile force causes the alveoli to open in cases of cong. laryngeal atresia (POTTER and BOHLENDER). It is obvious that there are still unknown factors in the mechanism which causes inflation of the lungs, and that it is not possible to solve these problems by way of an inflation mechanism.

With inflation of the lungs other phenomena also occur which help to elucidate the mechanism of expansion. One such phenomenon, simultaneous with the expansion of the alveoli, is the change in the circulatory pathway of the blood, which occurs when the fetal circulation changes. It is well known that during fetal life only a small quantity of blood passes through the pulmonary circulation. Only about 5 per cent (PARMELEE) of the total blood volume goes this way, while the greater portion

A relaxed capillary. An expanded capillary.

Fig. 1.

short circuits through the foramen ovale and ductus arteriosus directly into the left side of the heart. The function of the foramen ovale ceases actually before closure of the ductus arteriosus, which is believed to occur rather suddenly when the muscles, which form its walls, contract (BARCLAY). Henceforth the total blood volume has to pass into the pulmonary circulation. If the anatomical structure of the fetal pulmonary alveolus is considered, the following facts are revealed: the alveolus is atelectatic and it is surrounded by a dense capillary network, which is relaxed in consequence of the small quantity of blood within it. When blood flows into such a system, the capillary network expands, and my contention is that the opening of the pulmonary alveoli is due not to inflation, but to a *capillary erection which causes expansion of the alveoli*.

To test the feasibility of this theory experiments have been performed on the lungs of stillborn, fullterm and premature fetuses. In the preliminary experiments macrodex solution was injected instead of plasma into the a. pulmonalis of one lung and the other lung used as a control.

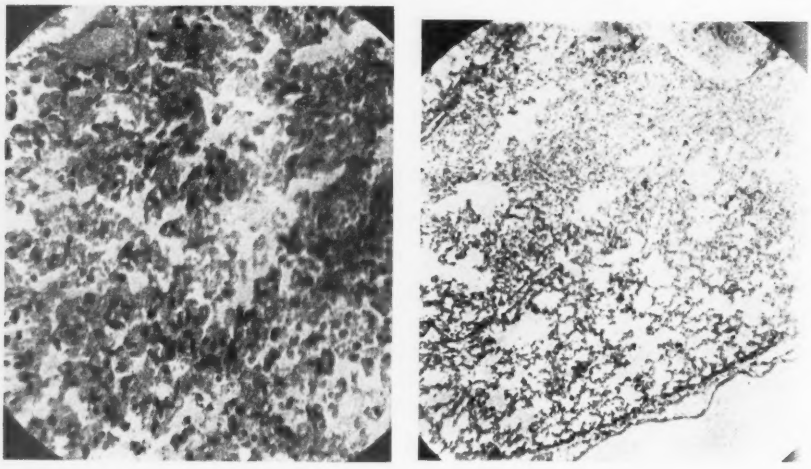


Fig. 2 A. Fig. 2 B.

A, reduced from a magnification of ×270; B, reduced from a magnification of ×60.

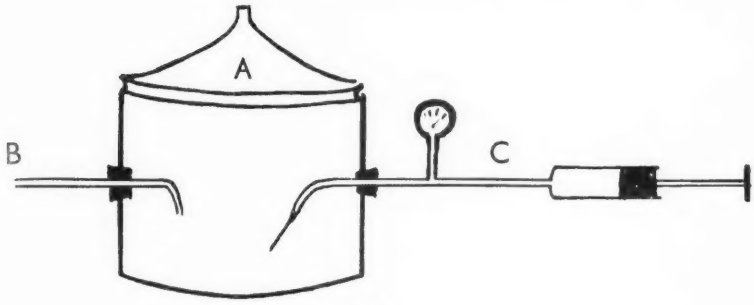


Fig. 3.

After three experiments the results looked promising. Although there was a completely atelectatic fetal lung in the control, the liquid pressure of the macrodex caused expansion of the alveoli in the other lung. The opening was to be found under the pleura visceralis. The difference in the amount of tension was also obvious, the most distal alveoli being most expanded. In a proximal direction towards the centre of the lung three transitional stages could be seen: well expanded alveoli, and alveoli with tortuous walls, and completely atelectatic tissue. The following photomicrographs are typical of this experiment (Fig. 2). Following this, the experiment was repeated under more physiological conditions. For this purpose a simple apparatus was designed, the construction of which will be clear from the drawing (Fig. 3).

A glass bottle was covered with a rubber membrane (*A*), which could be moved like a diaphragm by means of its central point. The glass tube (*B*), which ran through an airtight rubber stopper, was connected with the trachea. The glass tube (*C*), which also ran through a rubber stopper, was connected with an injection needle lying in a. pulmonalis. To the pressure-side of the apparatus a manometer was connected by means of a side tube in order to keep the liquid pressure within physiological limits (about 80 mm Hg). The lungs and the heart together were put into the apparatus. The macrodex was injected from the tube C into the a. pulmonalis of only one lung. When one imitated the movements of the diaphragm, the air flowed in and out, as in ordinary respiration. With this arrangement both a blood pressure and a respiratory equivalent were produced in one part of the lung, in the other part only the respiratory equivalent.

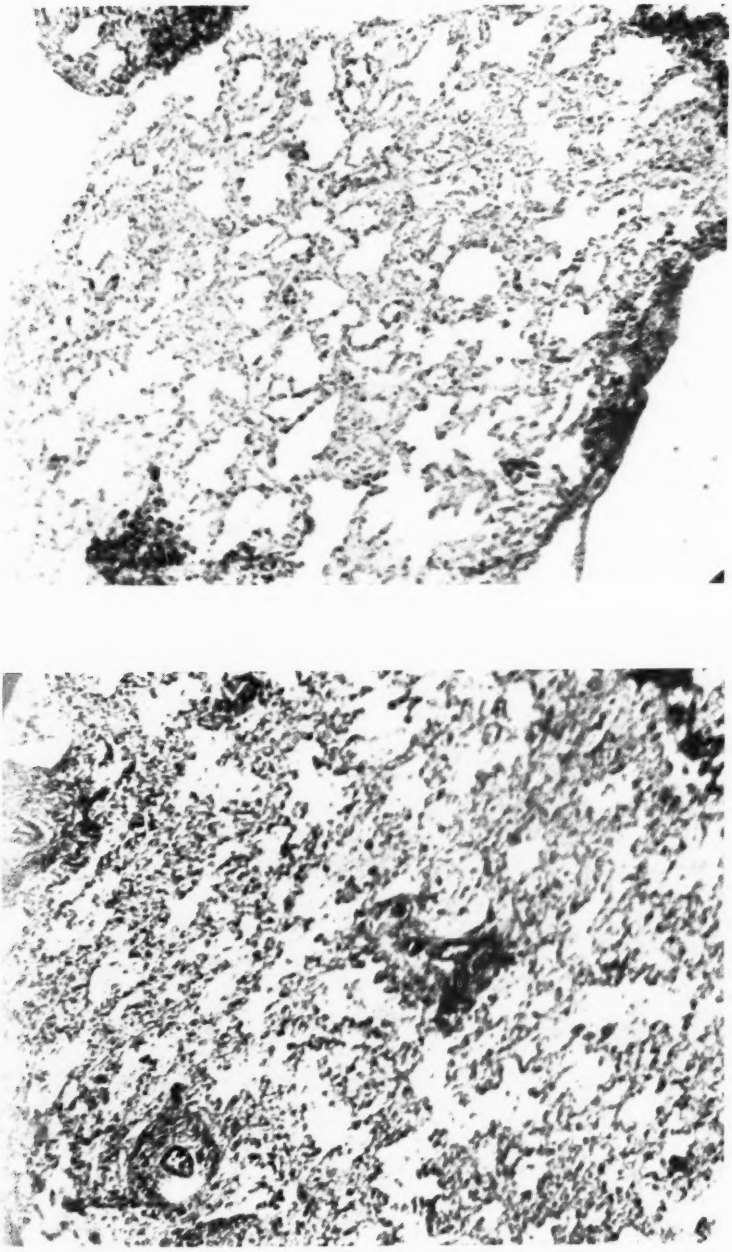
For this experiment the material was taken from a stillborn fetus. The cause of the intrauterine death of this fetus was unusual and significant, in so far as the result of this experiment went. The mother had run a nail into her foot, and had on this account received prophylactic tetanic serum. She then felt vigorous fetal movements, which ceased suddenly and were not felt again. The fetus was born dead 3 months later. Birth weight 2,000 g. The fetus was limp, and one could conclude from its appearance that it had been dead for a long time. The belief concerning the

cause of death of the fetus, is probably correct. The lungs were entirely airless, s
and light bluish red in color, resembling the thymus. Both lungs sank in wate

In the experiment it was significant that the movements imitati
respiration were at first rather slight and something seemed to occlu
the respiratory passages and prevent the movements. Suddenly, son
thing like an opening up occurred, and after that the respiratory mov
ments were similar, and deep on both sides. This obstruction of respirato
movement has appeared in the later experiments also. Perhaps a ph
nomenon of the like origin occurs in the newborn, in whom we often se
jerky obstructed respiratory movements, until vigorous respiratory mov
ments connected with the first cry render breathing easy.

It is to be noticed that the lung used in the experiment was very suit
able for the purpose. Firstly, it was like an empty sponge, from which
all the blood had drained, and secondly, there was no evidence whatso
ever to suppose that the alveoli had been inflated before birth, still les
after birth. In later experiments it has been proved that it is impossible
to obtain as good results with such material from premature fetuses or
from a fetus where intrauterine death has been due to interruption of
the umbilical circulation. The respiratory imitations were continued for
3–4 minutes, during which time the lung subjected to pressure, swelled
and looked somewhat oedematous. The result of the experiment was
very interesting. *The control lung still sank in water.* It fulfilled the con
dition that the child had not inhaled any air. *But the experimental lung,
which had been subjected both to liquid pressure and imitated respirator
movements, floated lightly on the water.* Thus it fulfilled also the condition
that the child had inhaled air. From this experiment it is obvious that
blood pressure plays a decisive part in the expansile mechanism of the
lungs. This experiment also explains why the alveoli do not expand in
utero although respiratory movements take place. The existence of the
ductus arteriosus and foramen ovale obtains a rational explanation in the
light of my theory. They are needed during fetal life, in order to inhibit
the initiation of the pulmonary circulation, otherwise the alveoli would
expand and the alveoli would be filled with liquid. Experiments have been
made by AHVENAINEN on animals, the results of which confirm my theory.
He experimented with kittens in vivo and noted that the alveoli opened
to a large extent during fetal aspiration of the amniotic fluid, if the pla
cental circulation is disturbed or interrupted.

Microscopic preparations were taken from both lungs. The microscopic
photographs of these are to be seen in Fig. 4 and 6. In both a number of
transverse sections of the alveoli and sacculi alveolares are seen. There is
one difference in the photographs that need a more detailed explanation.



B.

A.

Fig. 4. Photomicrographs reduced from magnification of ×60. A, the control lung. B, the experimental lung.

the section is cut through a sacculus full of air, there will be an openi
at the level of the section, which is seen in the picture as an empty circl
If, on the other hand, the sacculus is atelectatic or a little raised, the mic
tome cuts cellular elements also from the bottom of the sacculus and
the picture they can also be seen in the circle. The sketch below will e
plain this (Fig. 5).

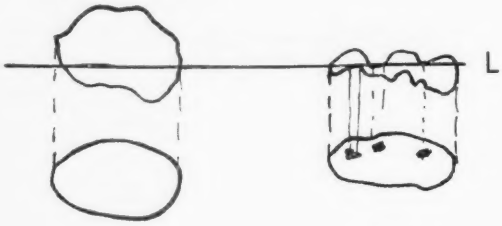
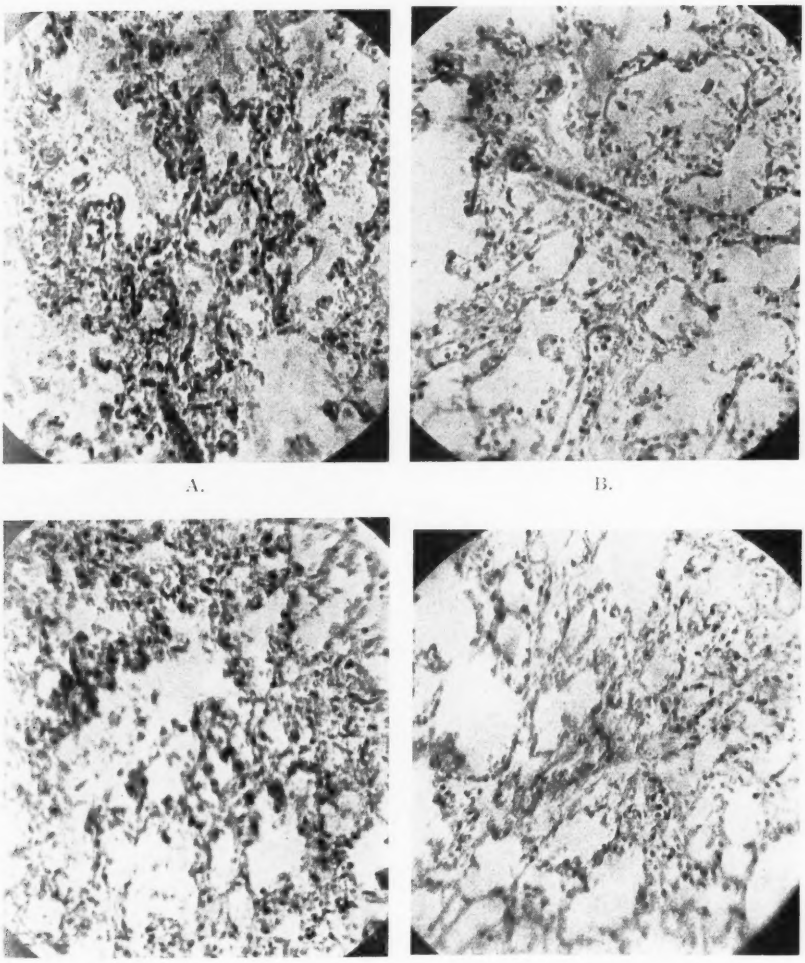


Fig. 5. A, the sacculus full of air; B, the atelectatic sacculus. L, the level of the section

From the photomicrographs it looks as though respiratory movement alone could raise the alveoli, as the photograph does not depict such a compact atelectasis as is found usually in primary atelectasis. Whether the mechanism of inflation acts as an aid when alveolar expansion occurs in vivo remains to be investigated. On the basis of my experiment it appears that the mechanism of alveolar expansion is mainly and decisively an erection mechanism and that inflation plays only a supporting, secondary part in it. That inflation alone cannot fill the alveoli is shown clearly by the floating experiment.

At this stage of my research, I obtained another preparation, on which I performed the same experiments, as on the former one. The preparation was from a premature fetus weighing 800 g and born dead after 6–7 months of gestation. The cause of intrauterine death was not clear.

During the experiment it is to be noted that the respiratory amplitude remained small all the time. STEWART's researches on young rats illustrate this fact. He has observed such plastic changes taking place in the pulmonary tissues that it would appear that they are prepared gradually for expansion. This of course would indicate a certain degree of maturity which one would hardly expect a premature fetus of 800 g to possess. After the routine experiment, I detached one lobe of the lung and injected macrodex into its artery, at a higher pressure than the normal physiological one. The reason for doing this was to investigate whether the purely mechanical phenomenon propounded by me occurred in spite of the rigi



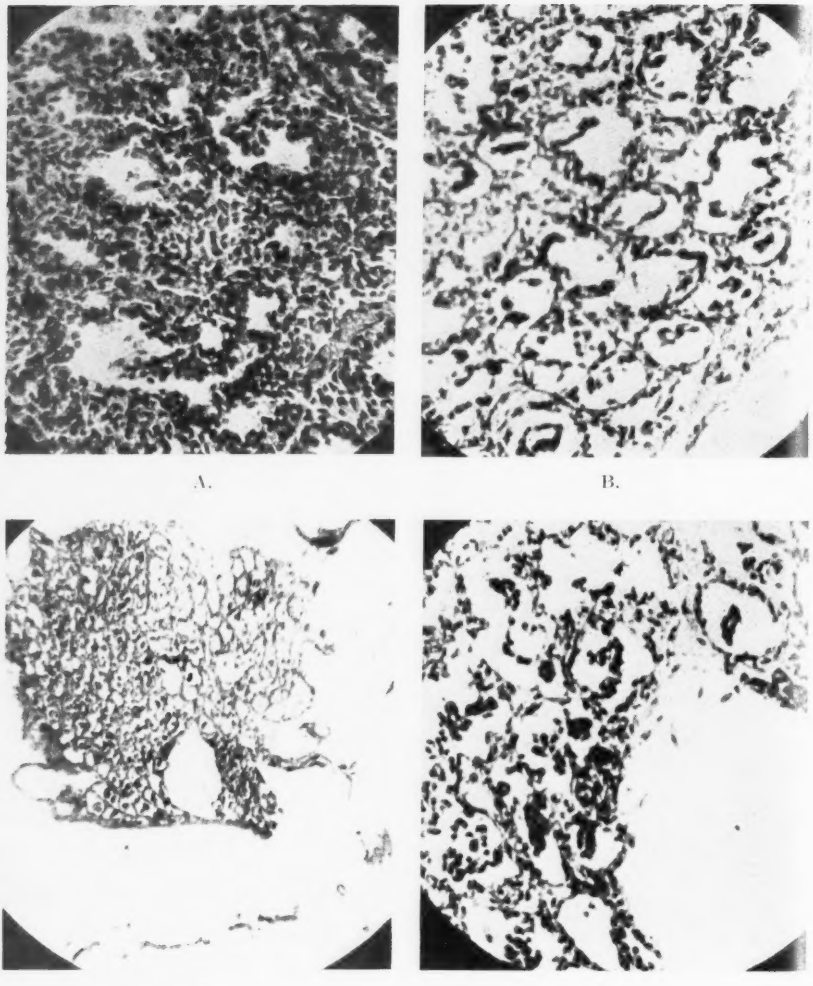
A. B.

A. B.

g. 6. Photomicrographs reduced from magnification of × 270. A, the control lung. B, the experimental lung.

y of the lung. Both parts sank in water both before and after the ex-eriment. The photomicrographs are to be seen in Fig. 7.

In the control part one can see typical fetal lung of 7 months' develop-ent (PATTEN). The epithelium is cuboidal. There is an open sacculus lveolaris during development, the "endbuds," the pneumoneres of which n be seen distinctly. In the experimental part opened alveoli were found



A. B.

C. D.

Fig. 7. A, the control lung; B, the experimental lung with physiological pressure; C and D the experimental part with higher pressure. A, B, D, reduced from a magnification of ×27 C of ×60.

in a small area under the pleura, and in the preparation with overpressure from a larger area. It is interesting to note that in the middle of almost every opened alveolus, there is a cellular conglomerate or a circle, which under higher magnification seems to consist of the cuboidal epithelium

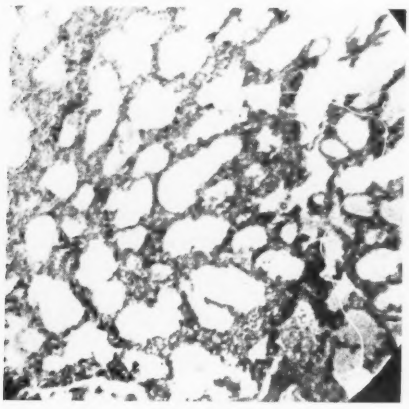


Fig. 8. Reduced from a magnification of × 60.

which lines the walls of the developing alveoli. Because so underdeveloped a lung is not ready to expand, the cuboidal epithelium has not been able to stretch sufficiently to follow the rapidly performed expansion, but has become detached and remained in the middle of the opened alveolus, often in the form of a circle.

It seems to me that even these photomicrographs support my theory. A picture of this kind occurs only if the alveoli are, as it were, opened up from the exterior and not inflated from the interior.

Theoretically, it seems quite possible to explain also the origin of asphyxial membranes in this way. It is easy to imagine that in vivo such a "pure" asphyxial membrane could have been pressed along the wall by the amniotic fluid and received elements also from it. Many other pathognomonic facts known in connection with the occurrence of asphyxial membranes would thus have a natural explanation. Asphyxial membranes appear most abundantly in immature fetuses and least abundantly in fully developed fetuses (AHVENAINEN), because in the former the lungs are not yet ready for expansion. Asphyxial membranes seem to be formed partly from the cells which cover the inner surface of the alveoli (AHVENAINEN). These membranes appear only in asphyctic children.

If air alone, flowing in, caused the expansion of the lungs, it should be easy to imitate it experimentally. FARBER and WILSON have used Drinker's respirator for this purpose. The photomicrograph which they show is similar to Fig. 8, which I have obtained from a preparation, the alveoli of which were inflated through the bronchus.

The result seems to be unphysiological and it does not resemble a microscopical picture of lung structure (MILLER), which is familiar to The tissue seems as if vacuolated, and the alveoli in it have pushed oth cellular masses aside by their own expansion.

Conclusion

A new theory to explain the opening mechanism of the lungs has be advanced: it has been proved experimentally that *expansion of the pulmonary alveoli is caused by capillary erection which is effected by the initiation of the pulmonary circulation.* The theory propounded does not contradict previous observations, which refer to the phenomena in fetal and neonatal lungs; these can be built into it and intricate problems, previously unexplained, may in it find a rational explanation.

The peculiarity of the fetal circulation has long been known, but an explanation for its function has not been produced. Such an explanation as: "The ductus arteriosus thus serves during fetal life as a means of balancing right and left cardiac output and in so doing, acts as what might be called the exercising channel of the right ventricle" (PATTEN), can hardly be sufficient. With the help of my theory the reason for the existence of the foramen ovale and ductus arteriosus, is explained quite easily. *They are indispensible in preventing the initiation of blood flow and the increase of blood pressure in the pulmonary circulation.*

I have not found this explanation of mine described in earlier literature and it should, consequently, be considered a new one.

Summary

Une nouvelle théorie sur le mécanisme du développement de la respiration chez le nouveau-né. Rapport préliminaire.

L'auteur propose une nouvelle théorie expliquant le mécanisme d'ouverture des poumons: Il a été prouvé expérimentalement que l'expansion pulmonaire était provoquée par la mise en tension des capillaires, laquelle est réalisée par l'apparition de la circulation pulmonaire. La théorie proposée n'entre pas en contradiction avec les observations antérieures, faites sur les poumons de foetus et de nouveaux nés. Il est possible de replacer tous les phénomènes dans son cadre, et même d'interpréter des problèmes n'ayant pas reçu jusqu'alors d'explications satisfaisantes. Les particularités de la circulation foetale sont connues de longue date, mais aucune explication satisfaisante de ses fonctions n'avait pu être donnée. Même, l'explication donnée ci-contre par PATTEN semble difficilement satisfaisante: «Le canal artériel a un rôle régulateur au cours de la vie foetale, de balancement entre les circulations droite et gauche, et peut en quelque sorte être appelé la voie d'exercice du ventricule droit». Grâce à ma théorie, la raison de l'existence du foramen ovale et du canal artériel s'explique clairement. Ils sont indispensables pour éviter le développement d'

courant sanguin et l'accroissement de la pression dans la circulation pulmonaire; il en résulterait en effet une mise en tension des capillaires, et une expansion alvéolaire, amenant la mort de l'enfant à bref délai après la naissance.

Eine neue Theorie über den Mechanismus des Atmungsbeginnes beim Neugeborenen. Ein vorläufiger Bericht.

Eine neue Theorie zur Erklärung des Entfaltungsmechanismus der Lungen wurde aufgestellt. Es wurde experimentell bewiesen, dass die Entfaltung der Lungenalveolen durch Erektion der Kapillaren bedingt ist, die durch den Beginn der Lungenzirkulation hervorgerufen wird. Die aufgestellte Theorie steht nicht im Gegensatz zu früheren Beobachtungen über fötale und neonatale Lungen, und man kann diese in die neue Theorie einbauen, sodass Probleme, die früher ungeklärt waren, nun eine rationelle Erklärung finden. Die Besonderheit der fötalen Zirkulation ist seit langem bekannt, jedoch hat man noch keine Erklärung für ihre Funktion finden können. Die folgende von PATTEN gegebene Erklärung kann kaum ausreichend sein, nämlich dass der Ductus arteriosus im Fötalleben seine Aufgabe in einem Ausbalanzieren des rechten und linken Herzschlagvolumens hat und dadurch als ein „exercising channel" des rechten Ventrikels dient. Mit meiner Theorie wird die Existenz des Foramen ovale und des Ductus arteriosus leicht erklärt. Sie sind unentbehrlich zur Verhinderung des Zirkulationsbeginnes und des Ansteigens des Blutdruckes im Lungenkreislauf, worauf eine Erektion der Kapillaren und eine Entfaltung der Alveolen im Fötalleben folgen würde, was nach der Geburt sofort zum Erstickungstod des Kindes führen würde.

Una nueva teoría concerniente al mecanismo de iniciación de la respiración en el recién nacido. Relación preliminar.

Una nueva teoría para explicar la apertura de los pulmones ha sido propuesta; ha sido probado experimentalmente que la expansión de los alvéolos pulmonares es causada por la erección capilar, que es producida por la iniciación de la circulación pulmonar. La teoría propuesta no contradice observaciones previas que se refieren a los fenómenos en pulmones fetales y en recién nacidos; complejos problemas previamente sin explicación, pueden encontrar en esta teoría una explicación racional. Las peculiaridades de la circulación fetal ha sido por largo tiempo conocidas, pero no se ha dado una explicación para su funcionamiento. Explicaciones tal como: «El canal arterial sirve durante la vida fetal como un balance entre el output del corazón derecho y del corazón izquierdo» (PATTEN) no pueden ser suficientes. En esta teoría las razones para la existencia del foramen oval y el canal arterial se explican facilmente. Son indispensables en prevenir la iniciación de circulación de sangre y el aumento de presión sanguínea en la circulación pulmonar, las consecuencias de las cuales serían una erección capilar y una expansión de los alvéolos durante la vida fetal, lo que conduciría sin duda alguna a la muerte del recién nacido.

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From the Medical Department, Children's Hospital, Gothenburg, Sweden

Prolonged Jaundice in the Newborn Associated with Congenital Myxedema. A Syndrome of Practical Importance

by Y. ÅKERRÉN

In congenital hypothyroidism or athyroidism (or congenital myxedema), early institution of therapy appears to constitute an important condition for successful treatment. The essential requirement for this is early diagnosis. Although the diagnosis is established occasionally in the first 3 months of life, the nature of the condition is, in the majority of cases, not recognised until later.

The fully developed picture of congenital myxedema is well known. The early symptoms are in the main the same as those encountered in the fully developed cases, though of lesser but of gradually increasing intensity. It is at this stage that the diagnosis is often difficult and even the experienced pediatrician, as will be apparent from the case histories which follow, may not infrequently miss the early diagnosis. Each pointer which can facilitate the early diagnosis of congenital myxedema, or tends to arouse suspicion of this condition is, therefore, of undoubted value.

The following case (Case 1) drew my attention to the fact that prolonged jaundice of otherwise physiological type (icterus neonatorum prolongatus) may occur in connection with congenital myxedema. It appeared later that the combination of congenital myxedema and icterus neonatorum prolongatus is of no great rarity. Thus, a further study of the literature and contact with colleagues, enabled me to collect in all 10 cases which will be presented and discussed here.

Case Histories

Case 1

Male infant, born Sept. 17, 51. Third child of healthy parents; siblings healthy. Born at term; delivery normal; birth weight 4.16 kg. Jaundice from the fourth day of life which later continued with approximately the same intensity. Urine and stools of normal colour. Defecation every second day. Entirely breast-fed; did not suck very well. Quiet and still. Cold hands and feet. Poor gain in weight. On Oct. 5, 51 the abdomen became distended and the following day more so. Admitted to

another hospital on Oct. 31. The combination of distended abdomen and jaundi was regarded as an indication for laparotomy. The stomach and intestines, part ularly the large intestine, were greatly distended. The liver and gall-bladder n mal. The abdomen was closed. On Nov. 1, 51 the patient was transferred to t Children's Hospital, Gothenburg. The child's physiognomy was immediately str ing with its wrinkled forehead with deep folds, deeply set eyes and large mou with protruding tongue. The skin was dry, cold on the hands and feet, not part ularly pale, but jaundiced as were also the sclerae. The genitalia, particularly t scrotum, were swollen and edematous. The patient's appearance is illustrated Fig. 1. X-ray of the skeletal system: only 3 centres of ossification were dem

Fig. 1. Case 1. $^{3}/_{11}$ 1951.

Fig. 2. Case 1. $^{24}/_{11}$ 1951.

strated (according to Elgenmark and Vickers-Harding, at least 4 should have be present). The ECG showed low voltage. No bile pigment present in the urine. Bi pigment content in the blood (Meulengracht): Nov. 1, 70; Nov. 9, 20; Nov. 13, 1 Dec. 12, 8. Bile pigment content in the blood (Jendrassik's method) 12.5 mg p 100 ml on Nov. 3. Direct reaction according to Hijman's van den Bergh's test neg tive. Apart from a pronounced hemoconcentration, no abnormality in the blo status on admission. Later, slight anemia developed (Dec. 4, Hb 60 %, R.B.C. 3. millions). The osmotic resistance of the red blood cells normal. Blood chemist normal, except for hyperchloremia on admission. Cholesterol content 70–99 m per 100 ml. E.S.R. normal. Prothrombin index on admission 45, later normal. Ser logical examination: infant's blood group O Rh(+), mother's blood group A_1Rh(− No irregular agglutinin in her serum. Coomb's test negative. Wassermann reacti negative in mother and infant. Acting on the diagnosis of congenital myxede with icterus prolongatus, a course of thyroid treatment was commenced from No 3. The meteorism and the jaundice diminished and disappeared gradually, the jau dice having disappeared by about the age of $7\frac{1}{2}$ weeks. The symptoms of congeni myxedema also disappeared rapidly. The child became more active and increas

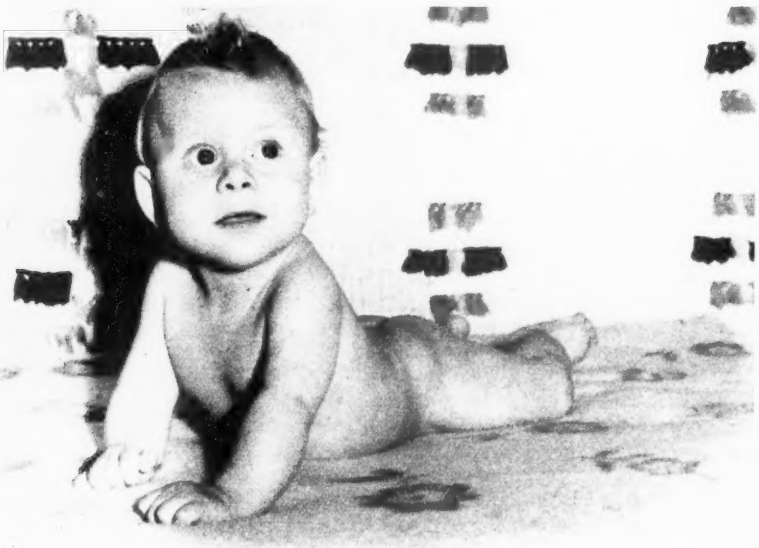

Fig. 3. Case 1. June 1952.

satisfactorily in weight. He has later developed satisfactorily in all respects. His habitus as at June 52 appears from Fig. 3. Gesell testings in Dec. 1951 and June 1952 showed normal psychomotor development. The development of the centres of ossification has become normal also.

Summary.—In a child aged 6 weeks, displaying an icteric pigmentation of the skin from the fourth day of life, rapidly increasing meteorism developed which led to the diagnosis of ileus, together with icterus of obscure origin. Laparotomy. At operation no abnormality of note was encountered, apart from great distension of the intestines, particularly the colon. On the day after operation, the patient was transferred to the Children's Hospital in Gothenburg, where the characteristic habitus of congenital myxedema together with cold skin etc. were noted. In addition, the diagnosis was supported by delayed development of the centres of ossification and ECG of low voltage. The successful treatment with thyroid confirms the diagnosis of congenital myxedema. The jaundice, observed from the age of 4 days, corresponds in all respects, apart from its duration, with the ordinary physiological icterus neonatorum. Mechanical obstruction of the biliary passages, hepatitis, lues, Rh-immunization and hemolytic icterus may definitely be excluded as causes of the jaundice, which regressed rapidly and disappeared entirely when the patient was between 7 and 8 weeks old.

Case 2

M.B., female infant, born Sept. 23, 46. First child of healthy parents. Admitted at the age of 6 weeks on account of poor gain in weight and persisting icterus which had developed immediately after birth. The infant was dull, with subnormal temperature (35.5° C), dry skin, large protruding tongue and hoarse voice. Constipation and umbilical hernia were not present. Icterus index (Meulengracht) 37. Hijmans van den Bergh's direct test negative. No bile pigment in the urine. Feces of normal colour. Blood status, including osmotic resistance of the red blood cells, normal. Blood cholesterol 186 mg per 100 ml. X-ray of the skeletal system revealed delayed development of the centres of ossification. After the institution of thyroid treatment, supply of heat by hot water bottles, previously required, could be dispensed with entirely. The appearance became normal and the jaundice disappeared. The subsequent development has not led to completely satisfactory psychic advancement, despite the early diagnosis and the continuance of therapy. The patient shows a pronounced convergent squint without any refractive error. This indicates a cerebral defect which is perhaps independent of the hypothyroidism.

Summary.—In this case also, everything seems to indicate that congenital hypothyroidism was causative, accompanied by icterus neonatorum prolongatus. No sign of hepatitis, lues, mechanical obstruction nor of abnormal hemolysis was present. Rh classification was not performed in this case. As the patient was the mother's first child and the blood values were completely normal, erythroblastosis may be excluded.

Case 3

E.K.J., female infant, born Sept. 14, 50. First child of healthy parents. Delivery and condition of the infant at birth normal; birth weight approximately 4 kg. Breast-fed. Admitted to hospital on Oct. 26, 50 on account of nasal discharge and subnormal temperature. The infant was jaundiced and had probably been so since the neonatal period, although the mother had not noticed this until the week prior to admission. The skin was coarse and dry, the abdomen distended and meteoristic, the voice hoarse, the facial features coarse with thick folds in the forehead and a large and frequently protruding tongue. X-ray examination showed delayed development of the centres of ossification (3 centres instead of the normal of at least 7 according to Elgenmark). The blood status showed normal condition on the whole. The osmotic resistance of the erythrocytes was reduced at the first examination probably on account of a technical error; later the resistance was normal. Blood chemistry normal. Blood cholesterol 128 mg per 100 ml. Icterus index (Meulengracht) varied between 35, 26 and 40 in the early tests but later the values diminished. The icteric pigmentation had disappeared about Nov. 5, 50 (at the age of approximately $7\frac{1}{2}$ weeks). The urine and feces were normal. The Wassermann reaction negative. Both mother and infant Rh( ). Thyroid treatment was instituted and led to improvement. Nystagmus became apparent early and persisted. The psychomotor development distinctly retarded. The persistent nystagmus, which is independent of any local defect of the eye, indicates a cerebral lesion which probably is indepen-

... of the thyroid deficiency. (The child returned for follow-up examination in June ...3 and proved to be somewhat backward with persistent nystagmus. Habitus ...erwise normal. Had been treated continuously with thyroid.)

Summary.—Symptoms, highly suspicious of congenital myxedema, were observed in a female infant who had jaundice of the prolonged physiological type until about $7\frac{1}{2}$ weeks old. Mechanical jaundice, hepatitis due to lues or other infection, Rh immunization, as also hemolytic icterus, could be excluded. Despite early thyroid treatment, which rendered the patient's habitus normal, delayed psychomotor development, probably due to a cerebral lesion independent of the thyroid insufficiency and manifesting itself, *inter alia*, by congenital persistent nystagmus, for which no local ophthalmological cause could be demonstrated.

Case 4

Concerning a case described by FINKELSTEIN, the following data are found.

Infant, aged 15 weeks. Normal weight; slight signs of hypothyroidism: thick tongue, hoarse voice, meteorism, constipation, umbilical hernia and anorexia. Distinct icterus from the neonatal period. No bile pigment in the urine. Feces of normal colour. Hb 65 %. R.B.C. 3.8 millions. Blood cells showed normal resistance. No increased number of nucleated red blood cells. No evidence of familial hemolytic icterus. During treatment with thyroid, rapid improvement of the hypothyroidism. Jaundice disappeared 3 weeks after commencement of treatment, i.e. at the age of 18 weeks.

Summary.—Although this case has not been examined meticulously, FINKELSTEIN's extraordinary powers of observation and experience, together with the clinical course, justify the statement that hypothyroidism, as well as icterus neonatorum prolongatus of the physiological icteric type, were concerned.

In the literature I later found a further case published by WALLGREN. This case was observed in the Children's Hospital in Gothenburg.

Case 5

E.I.K., male infant, born Nov. 6, 1940. First child of healthy parents. Normal delivery; birth weight 3.2 kg. From the third day of life, jaundice developed, increased and then remained unchanged for a prolonged period. Admitted to the Children's Hospital on Dec. 7, 1940 for investigation The child then appeared dull, temperature was subnormal and the abdomen large and meteoristic with an umbilical hernia as large as a pea. Marked jaundice also of the sclerae. Urine normal; did not contain bile pigment. Feces of normal colouring. Blood status including osmotic resistance of erythrocytes normal. No anemia. Icterus index (Meulengracht) Dec. 8, 121; Dec. 13, 71; Dec. 20, 49. The jaundice now began to regress and practically disappeared. It was also noted that the tongue began to increase in size. Wassermann reaction negative in mother and infant. The diagnosis of congenital myxedema was not made. The patient was readmitted at the age of approximately 3

months. (Icterus had entirely disappeared at the age of approximately 2 months.) Now the diagnosis of congenital myxedema was made immediately (large tongue, dry skin with cutis marmorata, distended abdomen, umbilical hernia, subnormal temperature, large face with small, deeply set eyes). The diagnosis was confirmed by the rapid effect of thyroid treatment.

Summary.—Typical case of congenital myxedema. Prolonged icterus of physiological type except as regards the duration. No criteria of lues, hepatitis nor other infection. No criteria of mechanical nor familial hemolytic jaundice. As the patient was the first child, this, in addition to the clinical course otherwise, does not favour the possibility of Rh-immunization. In his publication, WALLGREN employs the expression "jaundice of physiological type."

Through correspondence with Dr. M. D'AVIGNON, who at that time was in Paris, I learned about the following case.

Case 6

Female infant. The second of 3 children. The other two children and the parents healthy. Born somewhat prior to term following induction of labour. Delivery otherwise normal. At the age of about 3 weeks, the infant was medically examined and icterus of the physiological type was observed. The jaundice persisted stubbornly. On this account, thorough blood investigations were performed (I have not received the details of these) which did not reveal anything abnormal. The patient was re-examined at the age of about 2 months and showed persisting icterus, together with stubborn constipation and "ballottement abdominal vraiment énorme," so that megacolon was suspected. Further examination a fortnight later (at the age of $2\frac{1}{2}$ months) showed the same picture together with persisting icterus. After a further week, the icterus had disappeared and a typical picture of congenital myxedema was present.

Summary.—Although detailed data are absent in this case, there is scarcely any doubt that, here again, the combination of icterus neonatorum prolongatus and congenital myxedema was present. Meticulous and repeated examinations were performed and the patient was examined by a very outstanding and experienced clinician (Professor DEBRÉ of Paris, to whom I am greatly indebted).

I learned about a further case of this type while conversing with Professor VAHLQUIST of Uppsala, to whom I also express my gratitude.

Case 7

H.R.K., male infant, born February 7, 1939. The second child of healthy parents; the elder child healthy. Delivery normal; condition at birth normal; birth weight 4.3 kg. Admitted to hospital on account of icterus and bile-stained vomiting on March 18, 1939. The patient had slight jaundice together with slight rhino-pharyn-

genis. Otherwise nothing definitely abnormal was observed except a distended tense abdomen, together with an umbilical hernia approximately 1 cm in diameter. Urine normal; no bile pigment. Feces of normal colour. Blood status including determination of fragility of the erythrocytes showed no abnormality; no anemia present. Icterus index (Meulengracht): March 18, 33; May 5, 25; May 19, 5. Serum bilirubin according to Jendrassik-Cleghorn's method on May 5 3 mg per 100 ml. On discharge March 20, 39 it was noted that apart from jaundice, nothing abnormal was demonstrable. The infant was repeatedly examined in the out-patient department and was still jaundiced when next admitted on May 4, 1940. He had been dull and the weight had remained stationary. Now the typical habitus of congenital myxedema was demonstrable: broad nose with sunken bridge, thickened eyelids and narrow palpebral fissures, coarse skin, suggestion of cushioning on the feet, more marked cushioning on the sides of the neck. Cold feet. Pronounced cutis marmorata. On thyroid treatment, the patient became brighter rapidly and the icteric pigmentation had disappeared entirely by the end of May, at about the age of 4 months. The symptoms of congenital myxedema also regressed rapidly and the retarded psychomotor development began to improve.

Summary.—Here also the combination of icterus neonatorum prolongatus and comparatively slight myxedema, probably congenital, was concerned. The jaundice which lasted nearly 4 months did not differ in any way from physiological icterus except in duration. Mechanical and infectious causes could be excluded, as could jaundice of familial hemolytic type. Rh classification was not performed, but the completely normal blood values, obtained on the first admission, strongly militate against erythroblastosis as the cause.

After the completion of the foregoing account, I encountered 3 further cases in the literature, suggestive of the coincidence of congenital myxedema and icterus neonatorum prolongatus. The cases will be reported very briefly here.

Case 8

Published by B. Smeby (*Nord. med. 50*: 1304, 1953). Female infant, born June 1952. According to the case history, jaundice until the age of about 5 months. Development stopped at the age of 3 months. Examined in hospital at the age of months. The infant then displayed umbilical hernia, hoarse voice and dry, wrinkled, squamating skin. Body length approximately 11 cm less than average for that Treatment with thyroid caused rapid change of the habitus and increased psychomotor activity. The length increased by 8 cm in 4 months. Congenital myxedema been diagnosed also in an elder sister. The mother was Rh(−).

Case 9

This and the following case were published by Raymond Didier (*Arch. franç. Pat. 10*: 322, 1953). Male infant, born June 25, 1949. Normal at birth; had a relatively large cephalhematoma. Jaundice developed on the second day of life and

persisted without significant alteration until the age of about 4 months. Feces of normal colour. Very slow gain in weight and length, dull, listless and still. Examined at the age of $7\frac{1}{2}$ months. Showed in all respects the typical habitus of congenital myxedema. Both mother and infant belonged to blood group 0 and were Rh(−). Wassermann reaction negative. Relatively satisfactory somatic effect of thyroid therapy. Considerable delay in psychomotor development.

Case 10

Male infant, brother to the previous patient, born Jan. 31, 1951. Normal at birth. The mother had suffered from an attack of malaria during pregnancy, which was, however, adeviated. The jaundice developed on the third day of life and did not disappear until about the age of $3\frac{1}{2}$ months. Examination at the age of 19 days revealed nothing abnormal apart from the jaundice. On examination when the infant was nearly 6 months, the tongue was certainly large but otherwise nothing definitely abnormal was demonstrable. Examination of the centres of ossification was not carried out. Not until about the age of 7 months, and guided by a photograph, was thyroid treatment instituted. In this case also, the purely somatic effect of thyroid treatment was admittedly relatively satisfactory but the psychomotor development remained delayed during the entire period of observation.

Discussion

The diagnosis of congenital myxedema must be regarded as correct in the cases described above. Icterus neonatorum prolongatus was encountered in all.

The term icterus neonatorum prolongatus (YLPPÖ) has been employed for cases of icterus neonatorum with a duration of more than 2 weeks. The condition occurs most frequently in premature infants. DAVIDSON, MERRITT and WEECH state that physiological icterus may last 3 weeks. In an investigation at the Children's Hospital in Gothenburg, BESKOW found that among 946 infants, jaundice of physiological type with a duration of at least 48 hours occurred in 291, i.e. in 30.76 ± 1.50 per cent, while the mean duration was 11.37 ± 0.36 days with $\sigma' = 6.20$. From a statistical point of view, it seems very improbable that jaundice in a newborn infant with a duration of more than 30 days and still more, exceeding 42 days (6 weeks), is physiological in nature, in the proper meaning of the word.

Thus jaundice in a newborn infant with a duration of more than about 30 (11.37 + 18.6) days must be very rare under physiological conditions. Supported by this statistical analysis, it seems justifiable to draw the conclusion that icterus neonatorum prolongatus with a duration of 6 weeks or more, does not unconditionally merit the term physiological icterus. The term icterus neonatorum prolongatus of physiological type

has apparently been employed (e.g. by FINKELSTEIN and WALLGREN, cf. earlier) also for conditions of jaundice of remarkably long duration, obviously for the reason that the jaundice in question in all respects except duration, behaved like a physiological icterus neonatorum. FINKELSTEIN records, in addition to the case quoted previously, 2 further cases which he classifies in the group, icterus neonatorum prolongatus of physiological type. The cases are, however, investigated incompletely. In neither of those cases were symptoms nor signs of congenital myxedema encountered.

The diagnostic problem in icterus neonatorum prolongatus is complicated, primarily because there are no positive criteria of physiological icterus. In newborn infants who develop jaundice at the usual time, which runs a typical course and in which the duration of the condition is not too long—at the most 30 days—it may be said, when a group of cases is under consideration, that the jaundice, within a fairly large group, is with a high degree of probability of a physiological nature. When isolated cases are concerned, uncertainty occurs, particularly if the intensity or duration of the icterus deviates from the average. The diagnosis of physiological icterus neonatorum prolongatus must then be made per exclusionem. Thus, the absence of symptoms or signs of other types of jaundice, or of diseases which may be the cause of jaundice, becomes the decisive factor in support of the term physiological.

In none of the cases previously described was the patient examined until long after the development of the jaundice. The course and symptomatology were, however, undoubtedly those of the physiological type of jaundice except for the duration. As previously stated, the probability of Rh immunization as the cause is small, although this can only be excluded with absolute certainty in cases 1, 8, 9 and 10. There was no evidence of any other abnormality, as for example luetic or septic infection. The course and the symptoms speak strongly also against mechanical obstruction or infective hepatitis as causes.

Thus even if it seems justifiable to assume that the jaundice in the cases described here was of the physiological type, it is of interest to observe that it occurred, nevertheless, in association with a distinctly pathological condition, viz. congenital myxedema.

The simultaneous occurrence of these conditions, icterus neonatorum prolongatus and congenital myxedema, each of which is undoubtedly relatively rare, can scarcely be attributed to hazard or chance. The relationship must thus in all probability be causal. If this be the case, what is the nature of it? The following possibilities may be considered, viz.:

1) that the thyroid insufficiency is primary in relation to icterus neonatorum prolongatus,
2) that icterus neonatorum prolongatus is primary in relation to the thyroid disturbance, and
3) that both conditions are parallel and have a common cause.

Re 2. This possibility appears to be highly improbable. Were the icterus neonatorum prolongatus of physiological type this could hardly give rise to a thyroid insufficiency. Even if icterus neonatorum prolongatus were of pathological type, i.e. the expression of hepatitis of some sort, it would hardly give rise to thyroid insufficiency. As far as I know, no evidence is available that ordinary pathological conditions of icterus give rise to thyroid insufficiency.

Re 3. FRANCE, in cases of his recently published, illustrates the clinical and pathologico-anatomical picture of infection with salivary gland virus. In one of FRANCE's cases (No. 1), both a prolonged jaundice and a distinct thyroid deficiency with marked clinical symptoms were present. The so-called inclusion bodies were found in large numbers in both the liver and the thyroid gland (as also in other organs). In this case, particularly in the terminal phase, icterus indicated a grave hepatitis. The clinical picture thus differed greatly from that present in the cases I have described. To what extent milder cases of this type of virus infection occur is unknown; it is, of course, conceivable that these may occur. If so, FRANCE's case would at least indicate the possibility that an early thyroid deficiency and simultaneously prolonged jaundice—which must, however, be of hepatitis type—may have a common, infectious etiology.

Re 1. More pronounced thyroid deficiency involves a general prolongation of all processes of dissimilation, while the processes of assimilation remain intact. Increased glucose tolerance has thus been found in reduced thyroid function. Elimination of bilirubin from the tissues and the blood in physiological icterus may perhaps be regarded as a process of dissimilation which may be conceived as becoming prolonged in thyroid deficiency. It is also conceivable that the myxomatous nature of the tissues may cause the diffusion exchange from the tissue fluids, via the capillaries to the blood, and from the blood to the liver cells, to be delayed. BENDA states that the liver in cretinism seems to be smaller than might be expected from the size of the body.

Although the explanation of the relationship between icterus neonatorum prolongatus and congenital myxedema is, naturally, hypothetical, it seems most probable that the thyroid deficiency in these cases is primary in relation to the prolonged icterus.

A certain yellow pigmentation of the skin is stated to be characteristic of myxedema, also of the congenital type. This yellow pigmentation is said to be due to carotinemia. The differential diagnosis from true jaundice is made, *inter alia*, by the fact that yellow pigmentation of the sclera does not occur in carotinemia. However, it seems conceivable to me that the yellow pigmentation of the skin which has probably been observed also in a number of cases of congenital myxedema which were diagnosed early, was in certain cases a manifestation of true icterus and not only of hypercarotinemia.

How frequently congenital myxedema and icterus neonatorum prolongatus occur simultaneously, remains to be seen. The case histories, which I have presented here, indicate that icterus neonatorum prolongatus is not of any particular rarity in congenital myxedema. Recently, I saw a case of icterus neonatorum prolongatus with a duration of approximately 6 weeks, where nothing abnormal and particularly no thyroid disturbance could be demonstrated. FINKELSTEIN, as already mentioned, observed 2 cases of icterus neonatorum prolongatus where no apparent abnormality, hence no thyroid deficiency either, was observed nor demonstrated. As far as I have been able to ascertain, only VAHLQUIST has expressed himself concerning a relation between icterus neonatorum and congenital myxedema. He maintains that it is worth noticing that conditions resembling icterus neonatorum gravis apparently develop sometimes in infants with congenital disorder of the thyroid. He finds support for his contention in WALLGREN's case, quoted earlier, and also in case 7 which he had occasion to observe. In neither of these two cases had the icterus observed the character which distinguishes icterus neonatorum gravis, and further, no indication of anemia was present when the patients first appeared for examination. VAHLQUIST states also that he was so frequently informed of the presence of pronounced neonatal icterus, by parents of children in whom congenital myxedema was later diagnosed, that this could not be entirely a matter of coincidence. It is, possible, naturally, that VAHLQUIST is correct in this; personally, however, I am skeptical. Since I have become aware of the relationship between congenital myxedema and icterus neonatorum prolongatus, I have also sought information regarding the occurrence of pronounced or unusually prolonged neonatal jaundice in some patients with congenital myxedema whom I have had as patients or who have been referred to me for treatment. The answers have been negative or uncertain. Thus, from what has been stated here, the conclusion may be drawn that the relationship which seems to exist between icterus neonatorum prolongatus and congenital myxedema is probably not constant, i.e. that icterus neonatorum pro-

longatus and congenital myxedema in early infancy may occur independently of one another.

This is not surprising. In general it seems that congenital myxedema develops very insidiously and apparently with varying speed and intensity. A probable explanation of this is, as TALBOT and MORIARTY point out, the possibility that up to the time of birth, the fetus receives a supply of thyroid secretion through the placental blood which lasts for an indeterminate time and thus delays the appearance of symptoms. They maintain further that it is not inconceivable that this is supplemented later, by small quantities of thyroid secretion in the breast-milk.

Comment

From the clinical viewpoint, knowledge of the simultaneous occurrence of congenital myxedema and icterus neonatorum prolongatus is of practical significance. The occurrence of icterus neonatorum prolongatus of prolonged duration should thus motivate increased vigilance concerning possible symptoms or signs of congenital myxedema. To a greater or lesser extent, the occurrence of icterus neonatorum prolongatus tended to make the diagnosis of congenital myxedema difficult in cases 1, 4 and 5. Concerning case 4, WALLGREN states definitely that he was misled as regards the diagnosis of congenital myxedema, since attention was concentrated too much upon the condition of jaundice.

Summary

The author accounts for 10 cases of congenital myxedema with simultaneous icterus neonatorum prolongatus. From his series of cases and a critical analysis of the diagnostic criteria of icterus neonatorum prolongatus, the author draws the following conclusions:

(1) The simultaneous occurrence of two comparatively rare conditions, such as congenital myxedema and icterus neonatorum prolongatus of prolonged duration makes it highly probable that this is no chance coincidence.

The further nature of the relationship between these two disorders is discussed. The general inhibition of the maturing of the functions of the organs and the reduction of the rate of the metabolic processes which distinguish the newly born with deficient thyroid function, may explain why icterus neonatorum of unusually long duration can then occur. The possibility of an infectious origin, where both the thyroid gland and the liver are injured simultaneously, is also discussed. That this *may* occur, is shown by a case published by FRANCE, in which a virus infection simultaneously gave rise to lesions of the liver and of the thyroid gland with simultaneous jaundice and thyroid deficiency as sequelae. Such a pathogenesis was most probably not present in the cases described here.

(2) The syndrome of congenital myxedema and icterus neonatorum prolongatus of marked duration is of practical significance in drawing attention to the possibility of a thyroid deficiency and thereby facilitating an early diagnosis of congenital myxedema. Icterus neonatorum prolongatus is, however, probably no constant phenomenon in congenital myxedema.

(3) Icterus neonatorum prolongatus in the cases described here, appears to have been of the physiological type of jaundice. However, the term physiological should not be employed unreservedly in icterus neonatorum prolongatus having a duration of 6 weeks or more.

Association d'ictère du nouveau-né prolongé et de myxoédème congénital. Un syndrome d'importance pratique.

L'auteur rapporte dix cas d'association de myxoédème congénital et d'ictère du nouveau-né prolongé. De l'étude de ses observations, et de l'analyse des critères de prolongation de l'ictère du nouveau-né, l'auteur tire les conclusions suivantes: 1) La survenue de deux affections comparativement aussi rares, que le myxoédème congénital et l'ictère du nouveau-né prolongé, rend le fait d'une simple coïncidence peu probable. La nature du rapport entre ces deux affections est étudiée. Le retard de maturation dans le fonctionnement des divers organes, et la diminution des processus métaboliques, qui caractérisent le nouveau-né porteur d'un myxoédème congénital, sont des raisons susceptibles d'expliquer la durée anormalement longue de l'ictère du nouveau-né. L'auteur étudie la possibilité d'une atteinte infectieuse simultanée de la thyroïde et du foie. Une telle étiologie est possible, comme le prouve un cas publié par France, dans lequel une atteinte virale avait causé des lésions hépatiques et thyroïdiennes, laissant comme séquelles un ictère et une insuffisance thyroïdienne. Mais une telle pathogénie ne semble pas pouvoir être incriminée dans les cas ici rapportés. — 2) La connaissance de l'association possible de myxoédème congénital et d'ictère du nouveau-né prolongé semble d'une importance pratique. La durée anormale de l'ictère attire en effet l'attention du clinicien vers la possibilité d'une insuffisance thyroïdienne, et facilite de ce fait un diagnostic précoce de myxoédème congénital. La prolongation de l'ictère n'est pas cependant un phénomène constant, dans le myxoédème congénital. — 3) L'ictère prolongé observé dans les cas décrits, est du type de l'ictère physiologique du nouveau-né. Néanmoins, le terme physiologique ne semble plus pouvoir être employé pour un ictère dont la durée est de six semaines ou plus.

Ikterus neonatorum prolongatus vergesellschaftet mit kongenitalem Myxödem. Ein Syndrom von praktischer Bedeutung.

Der Verf. berichtet über 10 Fälle von kongenitalem Myxödem mit gleichzeitigem Ikterus neonatorum prolongatus. Aus seiner Serie von Fällen und einer kritischen Analyse der diagnostischen Kriterien des Ikterus neonatorum prolongatus zieht der Verf. folgende Schlüsse: 1) Das gleichzeitige Auftreten von zwei verhältnismässig seltenen Zuständen, wie dem kongenitalen Myxödem und dem Ikterus neonatorum prolongatus, lässt es wahrscheinlich erscheinen, dass es sich nicht um eine Zufälligkeit handelt. Die Art der Verwandtschaft zwischen diesen beiden Störungen wird diskutiert. Die allgemeine Hemmung in der Reifung der Organfunktionen und die Herabsetzung der Stoffwechselprozesse, die das Neugeborene mit mangelhafter Schilddrüsenfunktion auszeichnet, kann eine Erklärung für das Auftreten von Ik-

terus neonatorum mit ungewöhnlich langer Dauer geben. Es wird die Möglichkeit eines infektiösen Ursprungs diskutiert, bei dem sowohl die Thyreoidea als auch die Leber gleichzeitig geschädigt werden. Dass dieses geschehen kann, wird durch einen von France beschriebenen Fall gezeigt, bei dem eine Virusinfektion gleichzeitig eine Leber- und Schilddrüsenschäden führte, mit Ikterus und Schilddrüsenunterfunktion als Folge. Solch eine Pathogenese war höchstwahrscheinlich nicht in den hier beschriebenen Fällen vorhanden. — 2) Das Syndrom kongenitales Myxödem und Ikterus neonatorum prolongatus ist von praktischer Bedeutung, indem die Aufmerksamkeit auf die Möglichkeit einer Schilddrüsenunterfunktion gelenkt wird, wodurch die Diagnose kongenitales Myxödem erleichtert wird. Wahrscheinlich ist jedoch der Ikterus neonatorum prolongatus kein konstantes Symptom beim kongenitalen Myxödem. — 3) Der in diesen Fällen beschriebene Ikterus neonatorum prolongatus scheint von der Art des physiologischen Ikterus gewesen zu sein. Jedoch sollte der Ausdruck „physiologisch" nicht ohne Vorbehalt beim Ikterus neonatorum prolongatus mit einer Dauer von 6 Wochen und länger angewandt werden.

Ictericia prolongada del recién nacido, asociada con mixedema congénito. Un sindrome de importancia practica.

El autor da cuenta de 10 casos de mixedema congénito asociado con ictericia neonatorum prolongada. De su casuística y del análisis crítico del criterio diagnóstico en la ictericia prolongada del recién nacido, el autor desprende las siguientes conclusiones: 1) La presencia simultánea de dos cuadros patológicos relativamente raros, como el mixedema congénito y la ictericia neonatorum prolongada, hace pensar en que probablemente esta coincidencia no se debe al azar. La naturaleza íntima de la relación entre estas dos alteraciones es discutida. La inhibición general en la maduración funcional de los diferentes órganos y la disminución en la velocidad de los procesos metabólicos, que caracteriza al recién nacido con insuficiencia tiroídea, podria explicar la duración excesivamente larga de la ictericia neonatorum. La posibilidad de una etiología infecciosa, en que el hígado y la glándula tiroides fuesen afectados simultáneamente es también discutida. Que esto *puede* suceder, lo demuestra un caso publicado por France, en que una infección a virus dió origen a lesiones tanto del hígado como del tiroides, y a la aparición simultánea de ictericia e insuficiencia tiroídea. Tal patogénesis probablemente estaba ausente en los casos aquí descritos. — 2) El síndrome de mixedema congénito e ictericia prolongada del recién nacido es de importancia práctica al llamar la atención hacia la posibilidad de una insuficiencia tiroídea, facilitando de este modo el diagnóstico precoz de un mixedema congénito. La ictericia neonatorum prolongada no es, sin embargo, un fenómeno constante en el mixedema congénito. — 3) La ictericia neonatorum prolongada, en los casos aquí descritos, parece haber sido del tipo fisiológico de ictericia. Sin embargo la calificación de fisiológica no debe emplearse sin reservas en ictericias neonatorum prolongadas hasta una duración de 6 semanas o más.

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Electrocardiographic Changes in Measles

by ELIAS BENGTSSON and ANDERS BERGLUND

Myocarditis in measles is a rare complication. The changes which have been described previously have nevertheless been of a rather serious nature.

Eyster and Middleton found in a survey of the literature of 1896–1919 only one case of myocarditis in measles described. Lyon reported a case in 1946 of permanent complete bundle branch block arising during a measles infection in a 41-year-old patient. Clark found three cases of complete heart block in children with measles. Guistra and Nilsson described a case in 1950 where a five-year-old girl with measles suffered from pronounced signs of decompensation with cyanosis, dyspnoea, enlargement of the liver, tachycardia, falling flood pressure and an increase in the volume of the heart. The electrocardiogram on the first day showed supraventricular tachycardia with bundle branch block, the next day 2 : 1 A-V-block with bundle branch block, the third day A-V-block and bundle branch block. The patient was given digitalis and quinine and the electrocardiogram gradually became regular. X-ray of the heart showed a continuation of volume increase after the electrocardiogram had become normal.

Personal Investigation

Cases of measles are primarily admitted to the hospital because of complications, e.g., encephalitis, pneumonia or otitis occurring during nursing at home or else because of urgent social considerations. These odd cases come in all the year round, but special wards are opened to deal with larger epidemics. This happened during the years 1949–1952, and from these epidemics it has been possible to collect fairly uniform material.

The electrocardiographic examination was partly a routine examination by the standard leads once a week, the first being done during the first few days after admission to hospital. Since the length of treatment required for the majority of uncomplicated cases was 8 days, only one examination was usually made. If pathological changes were found, the ECG was followed by repeated examinations. On a consecutive material

consisting of 25 children, electrocardiograms were in addition taken once weekly over a period of five weeks; the patients then returned for check-ups. These 25 children have also been examined with unipolar leads (precordial positions 4R, 1–7, and aVR, aVL and aVF).

During the years 1949–1952, 737 cases of measles were admitted. Two hundred and eighty six of these did not have an electrocardiographic examination; the latter was carried out in those periods when there were the largest number of cases. Of the 451 cases examined electrocardiographically, 234 were uncomplicated and 217 complicated (with for instance otitis, broncho-pneumonia or encephalitis); in the groups that were not electrocardiographically examined the corresponding figures were 95 and 191. Four hundred and nine of the patients were children under 15 years of age, and 42 were adults. Patients with, or having recently had, other infections such as streptococcal tonsillitis and scarlet fever, or bacteriological complications from their measles, have been excluded from the assessment. Patients who had previously had any heart disorders have not been included in the examination.

Results

Of the 451 cases examined definite signs of electrocardiographic changes were noted in 8 cases, in 6 adults and 2 children.

Case 1. 36-year-old man. First week S–T elevation = 0.15 mV in leads I and II. Second week diphasic T_{II} and inverted T_{III}. Normal ECG the third week.

Case 2. 28-year-old man. First week variation of A–V conduction time by more than 0.07 sec. During the second week isoelectrical T_{II-III}. Normal ECG as and from the third week of illnes.

Case 3. Boy of 2, who had had otitis at five months of age, but otherwise been healthy. No heart disease in the family. On admission, heart and blood pressure normal. Towards the end of the first week ECG showed $S_{I-II} = 0.05$ sec. and QRS = 0.10 sec. During the second week $S_I = 0.07$ and $S_{II} = 0.06$ sec. R_{CR2} had M-configuration: thereafter unchanged picture for two months. The third month improvement of ECG: QRS = 0.09, $S_I = 0.06$ and $S_{II} = 0.05$ sec. The electrocardiogram remained unchanged during continuous observation over the next year. A soft systolic murmur and a split second sound were present over the base. Heart X-rays on admission showed normal configuration and volume = 178 ccm/m². During the second week a moderate general increase was observed, the volume was 230 ccm/m². A check one month later showed an unchanged state, but after another two months the volume had increased to 284 ccm/m² (Fig. 1).

Case 4. 27-year-old woman; had nodal rhythm the first week, sinus rhythm the second, but flat T_{I-II} and S–T elevation. Third week normal ECG.

Case 5. 24-year-old woman. During first week of illness isoelectrical T_I and mere indication of positive T_{II}.T_{CR6} negative. Towards the end of the first week T_{I-II} were negative as were the T waves over left precordium. Two weeks after commencement of illness completely regular ECG. Physical examination and blood pressure normal.

Fig. 1.

During the next month or so after discharge she was nevertheless troubled by tiredness and shortness of breath, found difficulty in climbing stairs and going uphill, and had attacks of tachycardia (Fig. 2).

Case 6. 28-year-old man. During the first week of illness isoelectrical T_{II-III}. During the second week positive T_{II} but flat T_I with S-T depression in the leads over the left precordium. Regular the third week.

Case 7. 6-year-old girl who during the first week of illness had isoelectrical $T_{I, II}$ but by the second week had a normal ECG.

Case 8. 38-year-old woman who was previously healthy apart from chronic asthmatic bronchitis. She was ill and short of breath on arrival, but had no heart trouble, nor any relative tachycardia. Towards the end of the first week of illness when ECG was taken for the first time, T_{II} was isoelectrical and T_I showed a mere indication of positive. The ECG became normal during the first week.

The electrocardiographic changes in these cases were considered significant. They were of short duration of 2–3 weeks in all cases except one, where an apparently permanent ventricular block developed. This resulted in a considerable dilatation of the heart; apart from this the clinical symptoms were few and far between. There were, however, at times periods of shortness of breath and signs of lowered physical condition during con-

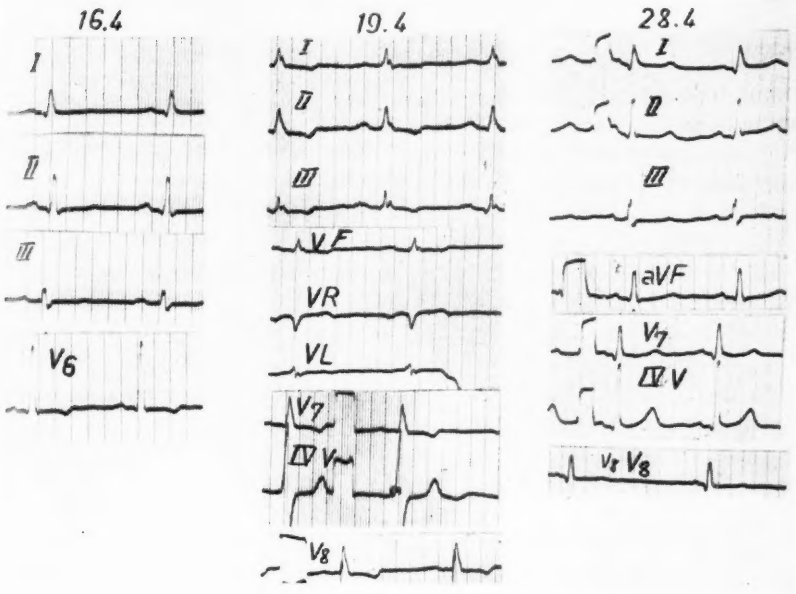

Fig. 2.

valescense. In these cases there was no evidence of the other complications of measles, intercurrent infections or previous heart trouble.

Of the 25 children who were examined with supplementary leads each week for five weeks, no electrocardiographic changes were found at any stage.

Doubtful cases. A number of other cases had temporary electrocardiographic changes, but did not fulfill the above conditions. A 4-year-old boy had during the second week nodal extrasystoles and at the same time a rough systolic murmur over the apex. He remained unchanged, however, during the whole period of nursing and observation. An 8-year-old girl, on admission, had auricular extrasystoles occurring regularly every 4th–6th beat, in the second week nodal rhythm and in the third week the same changes again. The arrhythmia remained for several months and was considered as a constitutional, possibly vegetatively incurred, disturbance of the rhythm. A five-year-old boy had temporary T-wave changes with isoelectrical T_{I-II}; at the same time, however, he had haemolytic streptococci in the nose and throat. Another boy with similar changes had no bacteria in the throat, but his antistreptolysin titre showed the following values during three consecutive weeks of nursing: 0–700–400 u/ml. A third boy also had pathological T-wave changes, but had had scarlet fever one month before contracting measles. Altogether there were fifteen of these more or less doubtful cases.

Conclusion and Discussion

The investigation showed that electrocardiographic changes in measles occur from time to time in adults, but only rather exceptionally in children. Electrocardiographic changes have had a short temporary course, but odd cases have shown signs of lowered physical condition during convalescence; these too, however, were of a passing nature.

It is perhaps remarkable that in earlier publications on measles the electrocardiographic observations were so pronounced and that even in this examination cases were found of acute bundle branch block running parallel with dilatation of the heart discernable by X-ray, and that the bundle branch block appears to have become stationary. The electrocardiographic changes have otherwise mostly consisted of temporary abnormalities in the terminal complex.

The occurrence of such complications as persisting bundle branch block in acute infectious illnesses should in many cases serve to explain why such changes are found from time to time in the examination of so-called "normal material."

The pathogenesis of myocarditis in virus illnesses is obscure. It is now well-known that viremia is present in certain virus illnesses. The highest frequency of myocarditis in poliomyelitis is in the bulbar paralytic cases, in which bacteriological infections of the air-passages, disturbances of the vegetatively regulated balance, and so on, undoubtedly have pathogenetic significance. What the situation is with regard to measles is not known, but in the encephalitic states which bring unconsciousness and lowered swallowing and breathing ability, the same mechanism as in bulbar paralytic states can probably be reckoned with.

Summary

In a study of measles, 451 cases were examined electrocardiographically. Of these 409 were children and 42 were adults; pathological electrocardiographic changes were found in 2 of the children (that is to say less than ½ per cent), but in no less than 7 cases in the adults (16.7 per cent). The changes were of a transient nature and lasted on an average 2–3 weeks, except in one case in which a right bundle branch block arose in a 2-year-old child and was still present one year later.

Modifications de L'ECG dans la rougeole.

Des ECG ont été réalisés chez 451 rougeoleux (409 enfants, 42 adultes). Des modifications ont été observées chez deux enfants (moins de ½ %) contre 7 cas chez les adultes (16,7 %). Ces modifications ont été passagères, et ont disparu en deux à trois semaines, sauf dans un cas où un block de branche droit est apparu, chez un enfant de deux ans. Il persistait encore un an plus tard.

Elektrokardiographische Veränderungen bei Masern.

451 Masernfälle wurden elektrokardiographisch untersucht, von denen 409 Kinder waren und 42 Erwachsene; pathologische elektrokardiographische Veränderungen wurden bei 2 Kindern gefunden (das ist weniger als $\frac{1}{2}$ %), jedoch bei 7 Erwachsenen (16,7 %). Die Veränderungen waren sehr flüchtig und dauerten durchschnittlich 2—3 Wochen, mit Ausnahme eines Falles, bei dem ein rechtsseitiger Schenkelblock bei einem 2-jährigen Kinde auftrat, der noch nach einem Jahr bestand.

Cambios electrocardiograficos en sarampion.

En un estudio de sarampion fueron examinados electrocardiograficamente 451 casos (409 niños y 42 adultos), se encontraron cambios electrocardiograficos en dos niños (menos de el dos por ciento) pero en 7 casos adultos 16,7 %. Los cambios fueron fugaces y duraron un promedio de dos semanas, excepto en un caso en que un block de rama aparecio en un niño de dos anos y persistio un ano.

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Congenital Pyloric Stenosis as a Factor Predisposing to the Ulcer Syndrome

by O. STEINICKE NIELSEN[1]

The question whether congenital pyloric stenosis may be a concurrent cause of subsequent gastric diseases has not yet been clarified. Before forming an opinion on this problem we must look at the etiology of congenital pyloric stenosis (cong. pyl. sten.).

Ever since Hirschsprung's statement in 1888 opinion has been greatly divided regarding the etiology of the disease, which still is not clear. It seems universally agreed, however, that there is found hypertrophy of the circular muscle fibres of the pyloric sphincter as well as spasm in the pyloric area. Some writers hold that the spasm is primary and the hypertrophy secondary, developing as a consequence of the increased muscular activity, whereas others take the hypertrophy to be the primary cause of the disease.

Adherents to the former theory base their view chiefly on the fact that the signs most often occur when the infants are a few weeks old. The result of an investigation by Wallgren (1946) likewise argued in favour of this theory. Wallgren submitted the stomachs of 1000 infants to X-ray examination a few days after birth and found normal conditions in all. Of these infants, five developed signs of cong. pyl. sten. about the age of 3 weeks, and renewed X-ray examination of their stomachs revealed a prolonged and narrow pyloric canal. Wallgren believed, however, that the changes in the pyloric muscles might very well have been present at birth, but have been too slight to cause signs or symptoms and to be demonstrable radiographically. Investigations in twins lend support to this point of view. Wallgren (1937) described a pair of dizygous, Lewis (1944) a pair of monozygous twins, of whom one had typical symptoms of pyl. sten., whereas the other had no clinical signs at all. However, X-ray examinations of the apparently normal twin revealed a hypertrophic pylorus.

Some writers adhere, as stated, to the view that the hypertrophy is the primary cause of the disease, and that it is present from birth. The cases in which infants operated on few days after birth already displayed hypertrophy of the pylorus argue in favour of this hypothesis. Meeker and De Nicola (1948) have given an account of a girl who when 2 days old developed signs of the disease and was operated on 2 days later. The girl's pylorus was already then markedly hypertrophic. It is un-

[1] Read before the Danish Pediatric Society, June 10, 1953.

hardly that spasm could have caused development of hypertrophy in the course of these few days. Further, LADD, WARE and PICKET (1946) state that pyl. sten. has been described in stillborn babies and in a 7 months old fetus.

Finally, some authors are of the opinion that an autonomic imbalance may be the primary cause of the spasm (BENDIX and NECHELES 1947). However, most modern writers probably regard the hypertrophy as the primary causative factor.

Next the question suggests itself whether this hypertrophy gradually disappears completely, or whether it persists to a certain extent and thus may be the direct cause of subsequent development of gastric diseases. Here, too, opinion is divided. MONRAD stated as his opinion that the disease is due to genuine hypertrophy of the pyloric muscles, and he believed, on the basis of a few cases submitted to post-mortem examination (the infants had died after the acute signs had ceased), that the hypertrophy persists through approximately the first year of life, then gradually disappears completely.

As mere investigations do not show that cong. pyl. sten. is not the primary cause of subsequently developing dyspeptic troubles, MONRAD (1928) therefore followed up 125 patients with cong. pyl. sten., of whom, however, only 11 were over 15 and only three over 20 years of age. He arrived at the conclusion, on the basis of this follow-up, that cong. pyl. sten. does not give rise to signs or symptoms later in life. HERTZ in his M.D. thesis (1915) arrived at a similar conclusion. RINVIK (1940) followed up 107 patients submitted to medical or surgical treatment, of whom, however, only seven were over 15 and none over 22 years old. He found a tendency to a somewhat higher incidence of dyspeptic complaints among individuals with previous pyl. sten. than MONRAD did in his cases. Similar studies have been carried out by TODD (1947) and AGOSTA and MARCHI (1948).

The above-mentioned results were all obtained on the basis of relatively short observation periods, which may give rise to erroneous conclusions, because possible dyspeptic complaints may not manifest themselves until adult life. An investigation carried out by BENDIX and NECHELES (1947) seems to bear out this view, these writers having found a greater tendency to underweight, nervousness, and peptic ulcer in individuals with previous cong. pyl. sten. than in the normal population. They followed up 17 patients operated on. The ages at the follow-up ranged from 18 to 28; 18 per cent of these had peptic ulcer or the ulcer syndrome.

If cong. pyl. sten. is able to cause gastric diseases in the adult life, the question suggests itself whether the developing signs and symptoms are of the same kind as those seen in pyl. sten. in adults, or whether they are of the nature of peptic ulcer and other gastric complaints.

The first problem arising is whether pyl. sten. in adults is a sequela of the congenital form. In trying to solve this problem G. RUNSTRÖM (1939) followed 107 children radiographically for some years. These chil-

dren had all had cong. pyl. sten. Sixteen were over 6 years of age, and the oldest 13. He classified the cases in three stages. The first stage coincides with the signs in babyhood. The second stage begins at the age of 12 months and lasts till about 4 years of age. Later the X-ray findings change, disappearing completely during the school years. RUNSTRÖM thinks, however, that a few adults may have persistent infantile hypertrophy, which may cause periodical signs and symptoms. A similar result was obtained by K. ANDRESEN (1940), who submitted 95 individuals, all between the ages of 1 and 17, to X-ray examination and observed many with X-ray findings suggesting hypertrophic pyloric stenosis, though the numbers decreased as age advanced.

According to the results of the above investigations we should not expect pyl. sten. in adults to be a sequela of the congenital form, though the two forms resemble each other anatomically and pathologically (G. REDELL 1947, ZETTERGREN 1947). In a few cases of pyl. sten. in adults this must, however, be supposed to be a sequela of cong. pyl. sten. (CHYMBLE and WALMSBY 1933, CROHN 1928, KATZ 1947, MCCANN and DEAN 1950, FENWICK 1953), as signs and symptoms of stenosis may develop after many years of freedom from such. MCCANN and DEAN divide hypertrophic pyloric stenosis in adults into two groups, namely an idiopathic form and a form attended by ulcer or chronic gastritis. The authors are of opinion that the idiopathic type at any rate is due to a subclinical form of the congenital hypertrophy, and that the other form possibly has the same etiological basis. As, however, cong. pyl. sten. in adults is an extremely rare phenomenon (KIRKLIN and HARRIS 1933, K. ANDERSEN, GAMMELGAARD and DE FINE LICHT 1946) it cannot, on account of this fact alone, be usual for cong. pyl. sten. to continue giving pyloric stenosis symptoms and radiographically demonstrable signs of pyl. sten. in adult life.

On the other hand, some doubt seems to prevail as to whether peptic ulcer or gastritis may develop later in life on the basis of cong. pyl. sten. MAYLARD (1904) claimed that chronic gastritis in fairly young individuals often is due to cong. pyl. sten. The question should possibly be considered whether continued, though mild, pyloric hypertrophy may cause inefficient emptying of the stomach and consequently be a causative factor in the formation of peptic ulcers (HORWITZ *et al.* 1929).

Present Investigations

In the hope of contributing towards a solution of the problem whether the incidence of peptic ulcer or gastritis is higher among persons who

have had cong. pyl. sten. than in the normal population I have followed up 95 individuals over 25 years of age who have all suffered from the disease.

These 95 individuals had in early infancy been admitted to a children's hospital suffering from cong. pyl. sten. They had all had the following main signs: weight loss, projectile vomiting, and visible peristalsis. The stay in hospital had been long (on an average 107 days).

It may be briefly stated that all the infants had been treated by gastric lavage, five also with atropine, and none had been operated upon.

The subjects examined comprise all the patients with cong. pyl. sten. admitted to Queen Louise's Children's Hospital from 1907 to 1922 (147 patients) and to the Children's Hospital at Fuglebakken from 1918 to 1927 (36 patients). This makes a starting series of 183 cases. Of these, 29 have died of their disease. The mortality rate was distributed over 5-year periods as shown in Table 1.

TABLE 1.

Mortality of infants admitted with cong. pyl. sten., grouped in 5-years periods.

Years	Number of patients	Number of deaths	Mortality %
1907–11	30	8	27
1912–16	50	10	20
1917–21	61	7	11,5
1922–27	42	4	9,5
Total	183	29	15,8

In addition to the above-mentioned 29 patients, nine died, according to the case reports, after their discharge from hospital, but none of gastric diseases. Moreover, on further inquiry, nine are stated to have died (two in early infancy within one month of discharge from hospital). No further information was obtainable on the causes of death. Nineteen subjects had to be excluded owing to deficient data (name and address), and in 22 cases the subject's address could not be found through the census register.

Ninety-five subjects are left, 73 men (77 per cent) and 22 women (23 per cent), who have all been followed up.

The follow-up examination was done by questioning about the subjects' present and previous states of health, especially about dyspeptic complaints. In contrast to American writers (BENDIX *et al.*), I did not ask about nervous or allergic symptoms. I endeavoured to make my ques-

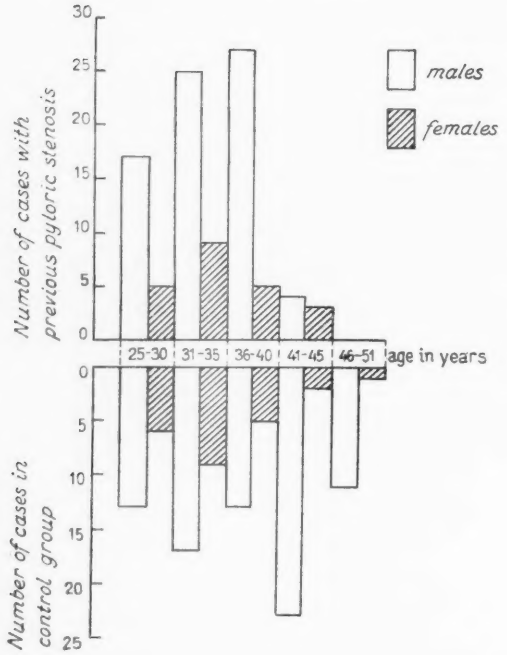

Fig. 1. Age distribution in starting series and in control group.

tioning as uniform as possible. Seventy-seven were questioned by personal conversation, eight by conversation with the nearest relations, the individuals concerned being absent, and finally, ten by means of verbally identical questionaries.

I thereby also procured information on the present weight and height. These figures accorded with the average weight-height figures for the adult Danish population. There seems, in other words, to be no signs of underweight among adults who have had cong. pyl. sten.

For comparison with the above series I have in a similar way questioned 100 non-selected hospitalized patients, 77 men and 23 women, of whom 75 were in the County Hospital of Copenhagen, Gentofte (Surgical Department), and 25 in Rudolph Bergh's Hospital (Dermatological Department).

The age distribution of the two series appears from Fig. 1. The graph shows that the control group comprised a greater number of relatively old subjects than the starting series. This may perhaps give rise to error in the assessment of the material. As, however, the incidence of dyspeptic

complaints rises with increasing age, this procedure can only contribute to raising the number of individuals with dyspepsia in the control group, a fact which does not invalidate the final result.

The patients of the control group had the following diseases:

The men: surgical lesions (fractures, wounds): 34, osteitis, panaritia: 9; varicosities, phlebitis, ulcer of the leg: 10; non-chronic skin diseases: 15; other diseases (epididymitis, varicocele, phimosis, venereal diseases, etc.): 9.

The women: abortion: 5, metrorrhagia: 7, varicosities: 3, surgical lesions: 4, other diseases (mammary hypertrophy, ovarian cyst, etc.): 4.

The subjects were thus chosen from among patients with widely differing diseases, and such as cannot *a priori* be supposed to bear any relation to gastric disorders. However, I fully realize that this group cannot be regarded as a proper normal series, as it is in some measure selected.

The results of the analyses of both groups appear from Table 2.

TABLE 2.

Classification of series according to dyspeptic complaints.

Number of cases in control group			Dyspeptic complaints	Number of cases in starting series		
f.	m.	total		f.	m.	total
21	57	78	never	18	37	55
1	3	4	in childhood only	1	7	8
0	6	6	mild	1	4	5
1	8	9	severe	2	20	22
0	3	3	peptic ulcer	1	4	5

The first three groups in Table 2, i.e. those with no symptoms, or symptoms in childhood only, or exclusively mild symptoms, are of no great interest. It is the last two groups that are of importance. In the last group but one I have included patients with pronounced gastritis to signs and symptoms of ulceration, that is, 22 in the starting series and nine in the control group. In the last group the diagnosis of peptic ulcer has been verified either by X-ray or operation. This group comprises five and three subjects respectively. By adding the two groups together it was found that among the individuals with previous pyloric stenosis 27 (28 per cent) had at least symptoms of gastritis, against 12 (12 per cent) in the control group.

There proved to be a slight tendency towards earlier onset of gastric diseases among the subjects with previous pyloric stenosis than in the

TABLE 3.

Symptoms of the 27 patients with severe dyspeptic complaints from the starti series.

No.	Age	Sex	Symptoms	Notes
7	42	M	Typ. ulc. sympts. for one year at age of 35	X-ray: pept. ulcer
14	39	M	Typ. ulc. sympts., last 2 years	X-ray: pept. ulcer
63	31	M	Typ. ulc. sympts., last 14 years	X-ray: pept. ulcer (1939)
64	31	M	Typ. ulc. sympts., last 10 years	X-ray: pept. ulcer (1942)
76	30	M	Typ. ulc. sympts. the last year	X-ray: pept. ulcer
1	45	M	Ulc. sympts. + vomiting from childhood	gastroduodenit (1931 & 42)
8	38	M	Epig. pain, last 2 years	hyperacidity
21	38	F	Ulc. Sympts. from childhood	no investigation
25	37	M	Periodical ulc. sympts., last 10 years	no investigation
30	37	M	Typ. ulc. sympts. the last year	hyperacidity
36	36	M	Ulc. sympts. from childhood	hyperacidity
39	36	M	Ulc. sympts. the last year	no investigation
42	35	F	Periodical ulc. sympts., last 7 years	no investigation
45	34	M	Ulc. sympts. from childhood	no investigation
67	31	M	Periodical ulc. sympts., last 11 years	gastritis (1950)
71	31	M	Ulc. sympts., last 13 years, 1 haematemesis	hyperacidity, X-ray: no ulc.
72	31	M	Typ. ulc. sympts., last 11 years	X-ray: no ulc. (1952)
75	30	M	Ulc. sympts., last 2 years	hyperacidity
81	30	M	Ulc. sympts., last 10 years	no investigation
84	30	M	Typ. ulc. sympts, last 9 months	no investigation
85	30	M	Periodical ulc. sympts., last 10 years	no hyperacidity
86	30	M	Ulc. sympts. + vomiting, last 10 years	no investigation
4	42	M	Ulc. sympts. betw. the ages of 35 and 37	no investigation
32	36	M	Typ. ulc. sympts. for one year at age of 35	no investigation
87	30	M	Typ. ulc. sympts. for one year at age of 28	no investigation
90	28	M	Epig. pain for 9 mo. at age of 22	gastritis (1946)
94	26	M	Epig. pain for one year at age of 20	gastritis (1946)
			Corresponding informations about the 12 patients from the control group.	
15	29	M	Periodical ulc. sympts., last 3 years	treated with Banthine
44	35	M	Ulc. sympts at age of 24	op. for ulcer (1943)
88	45	M	Ulc. sympts., last 25 years	op. for ulcer (1951)
10	28	M	Ulc. sympts., last 18 mo.	no investigation
22	31	M	Epig. pain for one year at age of 22	hypersecretion
33	33	M	Ulc. sympts., last 6 mo.	no investigation
45	35	M	Periodical abd. pain, last 15 years	X-ray: no ulc. (1938 & 50)
50	37	F	Periodical ulc. sympts., last 27 years	X-ray: no ulcer
53	37	M	Periodical ulc. sympts., last 10 years	no investigation
76	43	M	Periodical ulc. sympts., last 12 years	no investigation
81	44	M	Ulc. sympts. the last year	no investigation
92	46	M	Periodical ulc. sympts., last 2–3 years	gastritis

TABLE 4.

Number of cases of peptic ulcer and gastritis among the nearest relations of the subjects in the starting and the control group.

Control group			Number of cases among	Starting series		
total	gastritis	ulcer		ulcer	gastritis	total
100	3	3	Fathers	7	12	95
100	0	1	Mothers	3	3	95
319	6	2	Siblings	9	7	216
519	9	6	Total	19	22	406

control group. However, the difference in age at the onset of dyspeptic symptoms is not great.

The signs and symptoms of the 27 subjects in the starting series and the 12 in the control group are indicated in tabular form (Table 3).

Finally, I inquired from the subjects about possible known cases of peptic ulcer and gastritis among their nearest relations. The results are set out in Table 4, where ulcer means gastric or duodenal ulcer ascertained radiographically or by operation, whereas the diagnosis of gastritis is based mainly on subjective complaints.

Discussion

On the basis of the results obtained I have tried to assess whether individuals with cong. pyl. sten. are more liable to dyspepsia in adult life than normals, and also whether cong. pyl. sten. predisposes to the ulcer syndrome.

It is always difficult to assess a material based exclusively on subjective information, but the uncertainty is equally great for the present two groups. The same applies to the fact that gastric diseases are apt to be influenced by numerous extrinsic factors.

Interfering with the result is the fact that only just over half of the original 183 subjects were examined. These 95 cases do not constitute a well-defined group, neither with regard to the severity of the original disease nor with regard to social position at the time of follow-up.

Despite various sources of error the difference (28 per cent in the starting series against 12 per cent in the control group) must be said to be statistically significant.

Like MONRAD (1928), among others, I arrived at the result that the subjects rarely seemed to have been troubled while growing up by their disease in early infancy.

Forty-three of the cases under review had previously formed part of the series examined by MONRAD. Of these, three had then had dyspeptic signs after they had recovered from the acute illness.

No. 1, examined 6 years old: vomiting till the age of 1 year.
„ 2, „ 7 „ „ : „ „ „ „ „ 4 years.
„ 3, „ 9 „ „ : still vomiting.

Of these three, No. 2 is now in good health, whereas No. 1 has been suffering from typical signs and symptoms of gastritis and vomiting since the age of 20, and No. 3 likewise from gastritis since adolescence.

Thus, there is reason to suppose that cong. pyl. sten., after the acute signs have subsided, may develop in the following way, at least in medically treated patients:

As previously shown by X-ray examination of the stomach, by RUNSTRÖM (1939) and ANDRESEN (1940), among others, the hypertrophy of the pylorus persists for a shorter or longer period of childhood. That this hypertrophy does not give rise to dyspeptic complaints is explainable, among other things, by the fact that the exogenous factors which may be concurrent causes of gastritis are fewer in childhood than later on in life. The hypertrophy is believed, on the basis of X-ray examinations, to subside at the age of puberty at the latest. However, this has by no means been proved, so the possibility may be conceded that a latent hypertrophy persists in some patients, making these more liable to gastric and duodenal lesions later on in life.

Whether the incidence of gastric diseases later on in life will be the same for patients operated on as for medically treated patients cannot be determined on the basis of series of cases from this country until 10 to 15 years ahead, the observation period for the surgically treated infants being not yet long enough.

In addition to a tendency towards a higher incidence of dyspepsia in persons with previous pyl. sten. than in the normal population, the investigation has shown a considerable accumulation of peptic ulcer and gastritis cases among the nearest relations of the subjects with cong. pyl. sten. compared with the nearest relations of the controls. Though the material is small and though the assessment here, too, is based mainly on subjective information, the differences are so great as to justify the assumption of a certain accumulation of peptic ulcer in families with cases of cong. pyl. sten.

Summary

In order to study whether peptic ulcer and gastritis occur more frequently in individuals with previous congenital pyloric stenosis than in others, the author has questioned 95 individuals (73 men and 22 women) between the ages of 25 and 45, who had all in early infancy been treated medically for cong. pyl. sten. in a children's hospital. Information was thus obtained on the present and previous states of health of the individuals, especially on possible dyspeptic complaints.

Similarly a control group of 100 non-selected hospitalized patients (77 men and 23 women) between the ages of 25 and 51 were questioned.

In the starting series it was found that 28 per cent had gastritis or peptic ulcer against 12 per cent in the control group.

Adults with previous cong. pyl. sten. thus presented a higher incidence of gastritis and peptic ulcer than the control group. In addition, the investigation revealed a considerably higher incidence of gastritis and peptic ulcer among the parents and siblings of the questioned subjects in the starting series than among the corresponding relatives in the control group.

La sténose congénitale du pylore prédispose t-elle au syndrome ulcéreux?

Afin de déterminer si ulcère peptique et gastrite surviennent plus souvent chez des sujets atteints antérieurement de sténose congénitale du pylore, l'auteur a interrogé un groupe de 95 personnes (73 hommes, 22 femmes) agés de 25 à 45 ans, et traités pour une sténose congénitale du pylore au cours de la première enfance, dans un service de Pédiâtrie. On pouvait ainsi obtenir des renseignements sur l'état de santé actuel et antérieur de sujets, et notamment sur leurs troubles dyspeptiques.

Un groupe de 100 sujets pris au hasard, parmi des malades hospitalisés, et composé de 77 hommes et de 23 femmes, agés de 25 à 51 ans, a servi de groupe témoin.

L'auteur a trouvé 28 % de gastrite et d'ulcère peptique dans le groupe étudié, contre 12 % seulement dans le groupe témoin.

Le résultat de cette étude montre que les sujets ayant présenté une sténose congénitale du pylore sont atteints plus souvent de gastrite et d'ulcère peptique que ceux du groupe de contrôle. On note également une fréquence plus grande de la gastrite et de l'ulcère chez les parents et les collatéraux de la série étudiée par rapport à l'autre groupe.

Kongenitale Pylorusstenose als ein zum Ulcussyndrom prädisponierender Faktor.

Um festzustellen, ob Ulcus pepticum und Gastritis häufiger bei Individuen vorkommen, die früher eine kongenitale Pylorusstenose hatten, als bei anderen, habe ich 95 Individuen im Alter von 25 bis 45 Jahren (73 Männer und 22 Frauen) gefragt, die alle in früher Kindheit wegen kongenitale Pylorusstenose in einem Kinderkrankenhaus behandelt worden waren. Angaben über den gegenwärtigen und früheren Gesundheitszustand wurden erhalten, wobei auf eventuelle dyspeptische Beschwerden besonderer Wert gelegt wurde.

Gleichzeitig habe ich eine Kontrollgruppe von 100 nicht-ausgewählten hospitalisierten Patienten untersucht (77 Männer und 23 Frauen) im Alter von 25 bis 51 Jahren.

In der ersten Gruppe fand ich 28 % mit Gastritis oder Ulcus pepticum und nur 12 % in der Kontrollgruppe.

Das Ergebnis der Untersuchung war, dass Erwachsene mit früherer kongenitaler Pylorusstenose ein häufigeres Vorkommen von Gastritis und Ulcus pepticum zeigten als die Kontrollgruppe. Weiterhin hat die Untersuchung gezeigt, dass bei den Eltern und Geschwistern der betreffenden Individuen der ersten Gruppe Gastritis und Ulcus pepticum wesentlich häufiger vorkam als bei den entsprechenden Verwandten der Kontrollgruppe.

La estenosis pilorica congenita como un factor predisponente al sindrome ulceroso.

Para establecer si la ulcera peptica y la gastritis ocurren mas frecuentemente en individuos con previa estenosis pilorica que en otros, interrogue 95 individuos (77 hombres y 22 mujeres) entre las edades de 25 y 45, que habian tenido todos una estenosis pilorica tratada en un hospital durante la infancia.

Similarmente interrogue un grupo de control de 100 no seleccionados enfermos hospitalizados (77 hombres y 23 mujeres) entre las edades de 25 y 51.

En las primeras series encontre 28 por ciento con gastritis y ulcus peptico contra 12 % en el grupo de control.

Los resultados de las investigaciones eran que los adultos con estenosis pilorica previa presentaron una alta incidencia de gastritis y ulcus previo. Ademas la investigacion revelo una considerable mayor incidencia de la gastritis y ulcus peptico entre los padres de los sujetos de la primera serie con respecto a la serie de control.

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The Extracellular Fluid Volume in Infants and Children

by BENT FRIIS-HANSEN

During the last few years a number of papers have appeared on the measurement of the extracellular fluid volume by different methods. The results vary between 15–25 per cent in the adult human, but only a few determinations of this important body water compartment have been carried out in infants and children where a rapid decrease has been found during the first year of life, followed by a more gradual decrease during adolescence.

Theoretically the extracellular fluid includes all fluid outside the cells. It is not a rigid, well-defined "space" with exact boundaries, and both anatomical and functional sub-divisions exist, such as water in the serous cavities, cerebrospinal fluid and peritoneal fluid, and water in the gastro-intestinal tract and in the urinary tract. MOORE (10) has proposed the term "transcellular water" for the fluid in these areas.

Just as the extracellular volume is difficult to define, it is complicated to measure and no ideal method has been found so far.

An ideal substance for this determination should distribute itself evenly throughout the entire compartment without penetrating any cells, and should occur at a concentration equal to that in a plasma ultrafiltrate. Furthermore, this substance should not be metabolized or excreted until equilibrium has been attained.

A large number of compounds has been tried. These may be grouped as non-electrolytes and electrolytes.

The first group includes: inulin (25, 15), sucrose (6), and mannitol (28).

In the second group are: thiosulfate (16, 4), thiocyanate (5), bromide (38), sulfate (26), ferrocyanide (3), and lately radioactive compounds, e.g., chloride (41), bromide (8), sodium (20), and sulfate (39) have been used.

Of these, the "inulin volume of dilution" is accepted as the best estimate of the extracellular volume, but the technique is rather cumbersome as it requires a constant intravenous infusion for 4 to 6 hrs., and collection of the urine for the following 24 hrs. Consequently, the use of this method in infants is very limited.

Thiocyanate has been widely used (5, 9, 11), although later studies have proven that this substance penetrates into the cells during pathological states (30).

This investigation has been supported by a grant from the Carlsberg Foundation.

Lately a method has appeared where the extracellular fluid is determined from a single injection of thiosulfate. This substance was first used by KROGH (24) and in the human being by NEWMAN, GILMAN and associates (29, 16). It is non-toxic, diffuses rapidly, and does not exert any significant osmotic pressure at the low concentrations used. It is metabolized slowly but unfortunately excreted rapidly through the kidneys. The total rate of disappearance is however proportional to the concentration, and CARDOZO and EDELMAN (4) have shown that it is possible to calculate the "volume of distribution" from the disappearance curve, whereby values have been obtained that agree well with accepted values for the extracellular fluid volume.

It is the purpose of this study to evaluate this method in infants and children and to study the changes in the extracellular volume during growth.

In the same children, the total body water was determined by heavy water in order to estimate the intracellular volume which may be calculated by subtracting the extracellular water from the total. The result of this part of the study will be presented separately (14).

Material

The material consists of 50 children, ranging from newborn babies to 12 years of age. They were admitted to the department of pediatrics or born at the lying-in department *A* at Rigshospitalet, and were all considered to be in an normal state of nutrition and hydration. The determinations were usually carried out 4–6 hours after a light breakfast. Liberal drinking of tap water during the experiment was allowed in order to maintain a constant urine flow.

Method

For the determination of the extracellular volume, a 10 % solution of sodium thiosulfate (Pharmacopea Danica, 1948) (15.8 g of $Na_2S_2O_3$, $5H_2O$ and 6 g of sodium phosphate) were dissolved in 1 l destilled water and autoclaved in sealed ampules. This solution is stable for half a year or more.

Of this solution, 1.5 ml per kg body weight was infused intravenously at a rate of 1 ml per minute. The infusion was given with a calibrated syringe. A small rubber tube was inserted between the cannula and the syringe, whereby pain caused by changing of the needle was minimized and changing of the syringe facilitated. One ml of the same batch was diluted to 200 ml in a volumetric flask, thus making a standard solution of 50 mg %. The time was noted at the beginning of the injection and used as zero time. Blood samples were taken before, (plasma blank) and every ten minutes after the injection for the first hour, in small test tubes with heparin.

A fresh solution of 10 ml 10 % sodium tungstate and 10 ml $^2/_3$ sulfuric acid and 80 ml of distilled water was made up at each experiment and 4.9 ml transferred to centrifuge tubes to which 0.1 ml of plasma was added. After centrifugation, 2 ml of the supernatant was added to 2 ml of 1/1000 N potassium iodate in a broad test tube and 1 ml 2 N hydrochloric acid was added next. Five to ten minutes later 0.2 ml of a freshly prepared 10 % potassium iodine solution and three drops of a starch solution were added and the sample was then immediately titrated against a freshly made 1/2000 N solution of sodium thiosulfate. The latter was prepared from a 1/10 N solution, which is stable.

All determinations were carried out in duplicate.

The plasma concentration (C_p) is then calculated as

$$C_p = \frac{(\text{titration "plasma blank"} - \text{titration "plasma unknown"}) \cdot 98.75}{\text{titration "reagent blank"}}$$

and the standard (C_s) as

$$C_s = \frac{(\text{titration "reagent blank"} - \text{titration "standard"}) \cdot 98.75}{\text{titration "reagent blank"}}.$$

This is a micro modification of the indirect iodometric titration of NEWMAN and GILMAN (29).

The accuracy of this method may be calculated from the standard titrations where 50 mg % has been determined in 26 cases as 49.1 mg % with a standard deviation of 1.8 mg %.

In order to estimate the exactness of this micro modification, samples with known concentrations of 0 to 100 mg % were titrated. The results are shown in Fig. 1 where it is seen that determinations are correct only in the range between 3 mg % and 80 mg %.

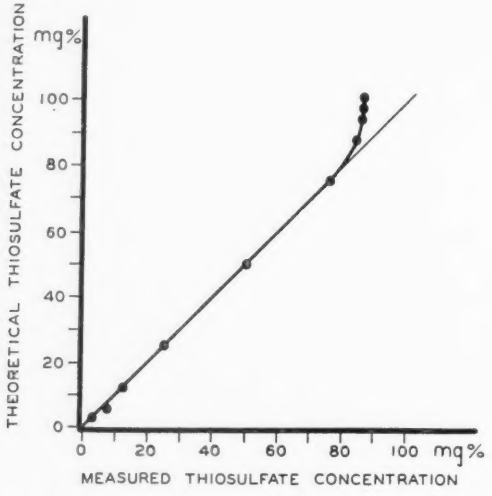

Fig. 1. The relationship between the theoretical thiosulfate concentration of different standard solutions and the values obtained by microtitration of these samples. Too low results are obtained at concentrations higher than 80 mg %.

Calculation of the Extracellular Fluid Volume

After injection, thiosulfate disappears rapidly from the blood at a rate proportional to its blood concentration, and when plotted on a semilogarithmic scale, the disappearance curve will form a straight line after equilibrium has been established (Fig. 2).

Theoretically equilibrium is never attained, because thiosulfate in the beginning of the experiment will move from the vascular bed out into the interstitial fluid as long as the blood concentration is higher, whereas the movement of thiosulfate will be in the opposite direction during the latter part of the experiment when the blood concentration is lower due to the rapid excretion.

Therefore the arterial blood concentration is higher than venous in the beginning of the experiment and lower afterwards (Fig. 3). Inulin is distributed in a similar way and comparison between the concentration of inulin in plasma and interstitial fluid has been made by SCHACHTER *et al* (35).

The main part of the injected thiosulfate is recovered in the urine, and the rest is metabolized. In children whose urine was collected for 24 hours after injection, two-thirds were recovered. This is the same fraction as found in the case of adults.

In order to calculate the extracellular volume, or rather "the volume of distribution," it would be necessary to know the concentration if all thiosulfate had been distributed evenly before any was lost. This ideal situation is, of course, never attained, as equilibrium is reached first some twenty minutes after the beginning of the infusion (zero time), at which one fourth of the amount injected already is lost. The theoretical concentration at zero time (C_0) may be determined, however, by extrapolation as shown in Fig. 2.

In order to calculate the concentration in plasma water (C_{pw}), the C_0 is corrected for the water content of the plasma. In most of the patients this has been taken as: 100 per cent minus the concentration of the plasma proteins in per cent, and in the rest of the cases as 93 per cent. The plasma proteins have been measured in a gradient tube (17).

The plasma water only constitutes one-fourth of the total extracellular fluid and the concentration in the interstitial fluid is unknown. Some investigators have stated that this fluid is a simple ultrafiltrate of plasma, and accordingly have applied a correction for the Donnan effect. Thus, GIBSON and associates (39), who have shown that radioactive sulfate offers an excellent substance for the measurement of the extracellular fluid, have taken the Donnan factor of sulfate to be the square of that

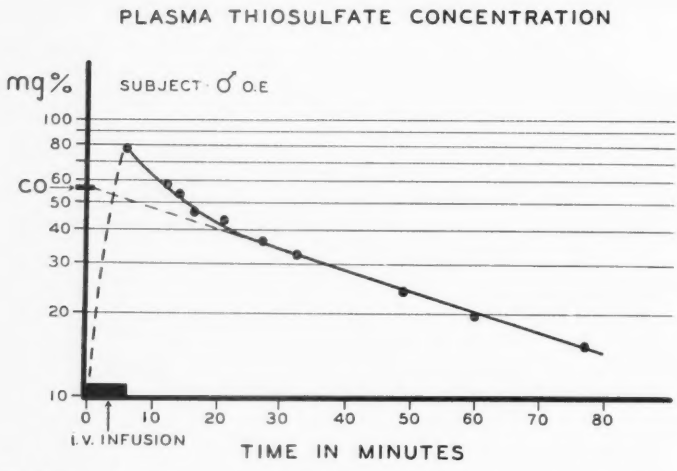

Fig. 2. The falling thiosulfate concentration after intravenous injection is plotted on a semi-logarithmic scale. At 25 minutes after injection equilibrium is reached and the curve becomes a straight line, that extraporated backwards will give CO, the theoretical concentration at zero time.

of chloride, or 0.90. Yet it is doubtful if this assumption is valid. In certain areas the lymph may contain 0.5 to 2 per cent of proteins, and, as the greater part of the "extracellular space" is occupied by hyalin substances, hyaluronic acids, muco-poly-saccharides, mucoitin-sulfuric-acids and chondroitin-sulfuric-acids, it seems unwise, although tempting, to apply such a correction. The overall effect of the above-mentioned acids may even act against the assumption that the plasma concentration is 10 per cent lower than that of the interstitial fluid in such a way that the reverse situation actually may exist. In this series, therefore, no correction for the Donnan factor has been applied.

The extracellular water volume (E) is calculated as

$$E = \frac{V \times C_s \times 200}{C_{pw}},$$

where V = the volume of thiosulfate infused, C_s = the concentration of the thiosulfate standard, and C_{pw} = the concentration of thiosulfate in plasma water at zero time.

The basis for this equation is discussed by NEWMAN and associates (8).

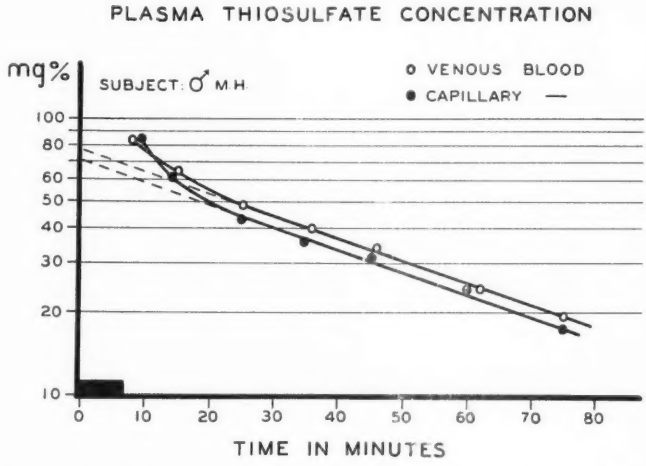

Fig. 3. A comparison of the concentration of thiosulfate in venous and in capillary blood shows that the capillary concentration is higher at the end of the infusion whereafter the venous will become the higher.

Results

The Curve

A typical curve is shown in Fig. 2. Equilibrium is attained at 22 minutes, at which time the curve becomes a straight line.

Determinations were carried out simultaneously in half the cases on venous blood and on capillary blood obtained from ear or heel puncture. Capillary blood, when freely flowing, is almost identical with arterial blood, and the concentration in heel blood was found in 6 cases to be almost equal to arterial obtained from the plexus of arterioles from the lateral malleolar artery (19).

The C_0 obtained from the capillary and the venous curves are not identical (Fig. 3), but as the capillary blood was assumed to give the most reliable picture of the overall clearance of thiosulfate, all calculations have been based on capillary blood.

In the pre-equilibrium period an excessive excretion of thiosulfate takes place as compared with the theoretical value, whereby an error is introduced. An attempt was made to study the magnitude of this loss by measuring the thiosulfate clearance during the first three 20-minute periods, and then comparing the difference between the theoretical and the actual excretion in the first period. Assuming that the clearance in period I was the same as in periods II and III, the theoretical excretion in period I may be calculated from the theoretical blood concentration (the extra-

polated curve) at 10 min. and the clearance. This was tried in 4 cases without any conclusive results, since the variations in clearance during periods II and III were greater than the difference between the actual and the theoretical excretion during period I. In most cases, also, the plasma concentration at 10 min. was only a few per cent higher than the theoretical value. Therefore, no correction for the extra loss during the pre-equilibrium period has been applied.

The effect of variations of the infusion time have been studied in dogs by RAISZ and associates (31). They found that a slow injection (10 min.) gave lower and more consistent results than a rapid injection (1 min.).

The ideal situation exists when the "incomplete" excretion of thiosulfate during the infusion (because the plasma concentration is below the theoretical value) is compensated by the "excessive" excretion preceding equilibrium (see Fig. 2).

The slope of the disappearance curve is the resultant of both renal and extra-renal losses, as it has been shown that the concentration of thiosulfate continues to decrease after nefrectomy in dogs (31). Furthermore the slope is determined by the proportion between the rate of removal of thiosulfate and the volume of the extracellular fluid.

In newborn babies a flat curve has been found, followed by a gradually increasing slope during the first year of life. The slope may be expressed as per cent per minute (28) and the following average values have been calculated in the different age groups: 1 day, 0.25 per cent; 1 month, 1.10; 1–4 months, 1.40; 6–12 months, 1.58; 1–2 years, 1.61; 2–3 years, 2.13; 3–5 years, 1.92; 5–9 years, 2.00, and 9–12 years, 1.89 per cent per minute.

This agrees well with both the well-known immaturity of renal function during infancy and the relatively large volume of extracellular fluid in infants.

Equilibrium Time

This was determined from the curve as stated above. In most cases equilibrium was reached in 15 to 20 minutes, but, in a few of the youngest cases, not until 30 minutes.

Deviations in the Curve

In some cases the disappearance curve did not become a straight line; more or less pronounced deviations from linearity were seen. A typical example is shown in Fig. 4, where both capillary, arterial and venous blood was followed. In this case, no decrease in concentration was found even from 30 to 40 minutes. This is difficult to explain. Theoretically, three possibilities exist:

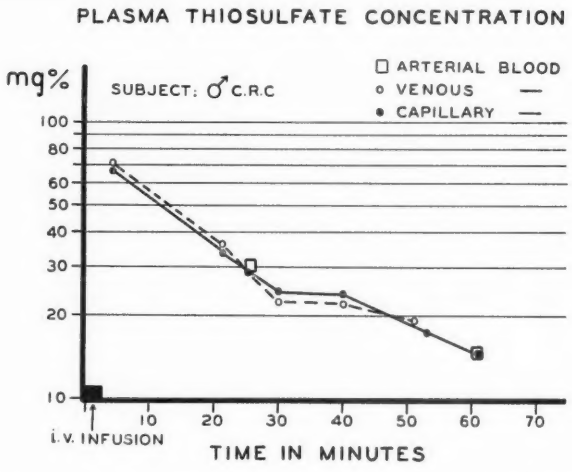

Fig. 4. In this patient the concentration of thiosulfate was followed in both arterial, capillary and venous blood. The significance of the flattening of the curve seen between 30 and 40 minutes is discussed in the text.

(1) A temporary stoppage or decrease in the renal excretion. Such changes have been observed after painful stimuli, although to a much lesser extent (40). It may be noted, furthermore, that the renal clearance remained constant during the three twenty-minute periods in a similar case, which makes this possibility unlikely.

(2) Movements of water, from one phase of the extracellular phase to another from which thiosulfate is excluded, would produce an increasing concentration within the first phase. The greatest volume changes found in normal conditions are related to secretions into the gastrointestinal tract, which total 8 l daily, or two-thirds of the total extracellular fluid. It was found that the gastric juice only contained a few mg% of thiosulfate during an experiment where histamin secretion was induced 20 min. after infusion, and no constant break was found in the curve, after histamin injection. An increased concentration (or lack of decrease), as that shown in Fig. 4, would correspond to a shift of 25 per cent of the extracellular water, a value so high that it seems unreasonable to believe that this is the explanation.

(3) The third possibility is the occurrence of reopening of circulation in certain areas of the body, where the circulation has been temporarily slowed down at a time when the blood concentration was high; thus, a dep effect would be exercised by this part of the body. A somewhat sim phenomenon was noted in a previous work (36) where an increasing

TABLE I

The age of the subjects in the groups are given in days (d.), months (m.) and years (y.) and the extracellular fluid in liters, as per cent of body weight and as liters per square meter.

No. subjects	Age	Weight kg	Surface area m^2	Extracellular fluid		
				liters	per cent body wt.	liters per m
4	1 d.	3.49	0.216	1.54	44.1	7.13
4	1 m.	3.29	0.203	1.31	39.8	6.45
2	1– 2 m.	3.67	0.218	1.25	34.0	5.74
3	2– 6 m.	4.61	0.258	1.40	30.4	5.63
6	6–12 m.	7.78	0.368	2.08	26.7	5.65
4	1– 2 y.	11.66	0.478	2.97	25.5	6.21
8	2– 3 y.	13.16	0.561	3.51	26.7	6.26
3	3– 5 y.	16.27	0.687	3.81	23.4	5.55
11	5– 9 y.	24.33	0.916	5.09	20.9	5.56
5	9–12 y.	35.12	1.198	6.90	19.6	5.76

venous blood concentration was found for as long as 45 minutes after a single injection of heavy water, presumably due to a slow circulation in the arm from which the blood was drawn.

The circulation in the subcutaneous tissues and the splanchnic circulation is known to be subject to great variations. In order to determine whether changing skin temperature might cause any breaks in the curve, an experiment was performed where both arms were packed with ice between twenty and forty minutes after injection, followed by application of heat and massage. This did not have any effect on the curve.

So far, no explanation of this deviation of the curve has been found, and several factors may be operating at the same time. When it occurs, the experiment is a failure since it is then impossible to make any valid extrapolation. Fortunately, this only happens in a few cases.

Deviations in the curve are to be found in the papers of other investigators (4, 29), but no explanation has been given.

Reproducibility

The reproducibility of the method was tested in three subjects. In these experiments the difference between the paired determinations were 1.4, 2.8, and 0.3 per cent, when expressed as per cent of body weight. In the adult patient, however, determinations before and during ACTH therapy gave inconsistent results (12).

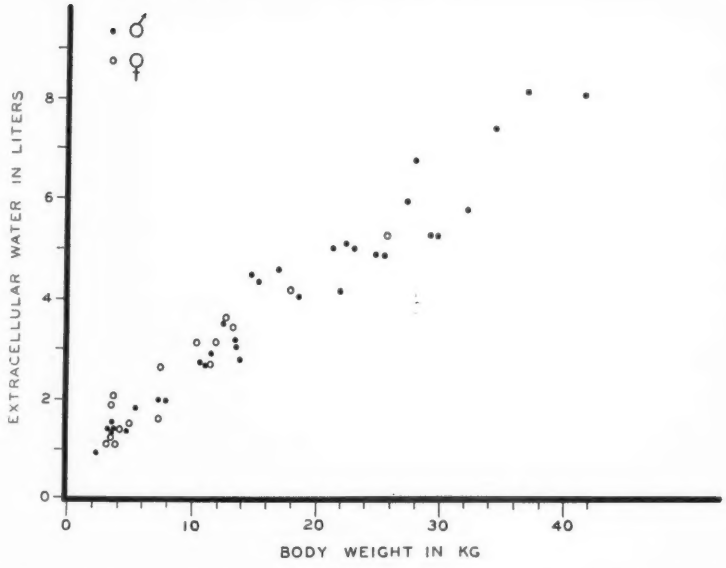

Fig. 5. The relation between body weight in kg and extracellular fluid in liters. No difference is found among female and male subjects.

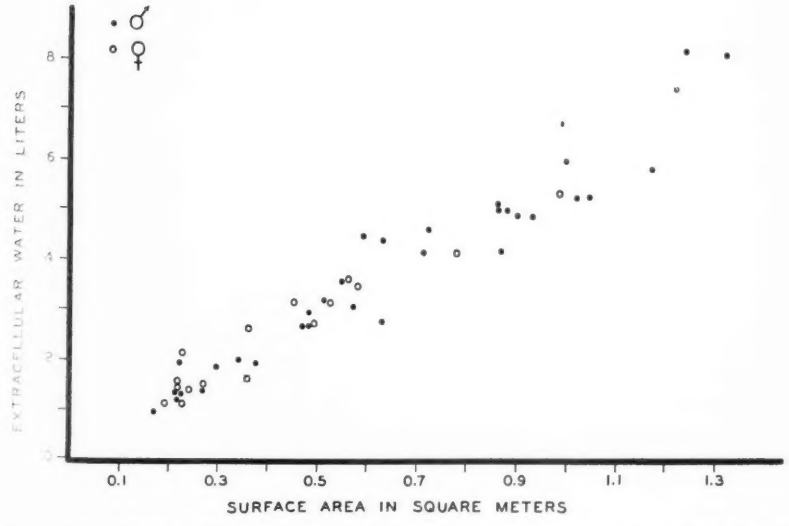

Fig. 6. The relation between surface area in square meters and extracellular fluid in liters. This relationship also shows no sex difference.

The Extracellular Fluid Volume

The results of the determination of the extracellular volume, measured as the volume of distribution of thiosulfate, is given in Table 1. The data are expressed in liters, in per cent of the body weight, and in liters per square meter. Values higher than 50 per cent of body weight are found in newborn babies, and a rapid decrease is observed to take place during the first two months of life, followed by a less pronounced decrease during the first year. A gradual decrease continues until adult values are reached around puberty.

When expressed as liters per square meter the decrease is less pronounced and mainly found during the first month of life. No difference is found between males and females as shown in Figs. 5 and 6, in which the extracellular volume has been plotted as a function of weight and of surface area.

Discussion

The Method

Some limitations of the method have been discussed above. The underlying principle is that thiosulfate does not penetrate into the cells and is evenly distributed extracellularly. This has never been proven directly, but the assumption is based on several observations. Thus, thiosulfate is distributed in a volume close, or equal, to the extracellular volume as estimated by other methods (4, 16, 24, 29, 31). Moreover, the "thiosulfate" volume has been shown to vary in a manner explicable in terms of simultaneous changes induced in the extracellular volume (4). The thiosulfate ion is not secreted by the tubular cells of the kidney (2), or at least to a minor extent only (except in the cat (1)), and is not secreted by the gastric glands. On the other hand, thiosulfate does permeate into the erythrocytes (4, 23), but the resultant error introduced is so small and inconsistent that no correction has been applied for it. Finally, thiosulfate is not bound to proteins (23).

Previous Work

Most other observations of the extracellular volume in children have been carried out by the thiocyanate method (5), although it has been shown repeatedly that thiocyanate ion is bound to protein and lipids (34, 37). Moreover, thiocyanate is taken up by glandular cells and is found in most secretions in the same concentration as in the blood, and figures obtained by this method are 5 to 10 per cent higher than the generally accepted value for extracellular volume, 14–17 per cent of the body weight.

During fevers the "thiocyanate dilution space" expands to values almost equal to the total body water (30), presumably due to changing cellular permeability. These facts have been taken into account by the various investigators who, nevertheless, have used this method because of its simplicity, relying on the assumption that, under normal conditions, the "thiocyanate dilution space" is a close approximation of the "functional chloride space".

The greatest numbers of subjects have been studied by ELY and SUTOV (9). Their results, in different age groups, were as follows: 0–½ year, 39.3 %; 0.6–1 year, 32.9 %; 1–2 years, 31.9 %; 3–5 years, 29.9 %; and 5–15 years, 29.1 %. A similar rapid decrease during the first half year has been observed by FELLERS and his co-workers. These values are in agreement with other observations (7, 18, 22, 32, 33), with the single exception that MORSE (27), in 65 children, did not find that the thiosulfate volume decreased with increasing age; but this may be explained partly by the fact that his youngest subject was 3 years of age. It is of interest to note that the results in infants cited above are in close agreement with those obtained in the present study, and higher in children although it has been observed in the case of adults that the thiocyanate volume is 5–10 per cent higher than the corresponding thiosulfate volume.

A few determinations of the extracellular volume in children have been carried out by other methods. Inulin was used by KATCHER (21), and lower results were obtained: 1½–2 months, 26 %. The Na-24 space at 2½–4 hours after injection (11, 13) has been found to be slightly larger than the thiocyanate space.

Summary

The extracellular volume in fifty infants and children has been studied by a micro modification of the thiosulfate method. This technique was first tried out and it was found that determinations carried out on capillary blood gave the most consistent results. Some limitations of the method are discussed.

The extracellular volume was found to diminish rapidly during the first six months of life, from 44 to 30 per cent of body weight, later a gradual decrease during childhood ensued, from 30 per cent to 20 per cent around puberty. When expressed as liters per square meter surface area of the body a less pronounced fall was observed, and only during the first month of life.

Le volume des liquides extra-cellulaires chez le nourrisson et l'enfant.

Le volume des liquides extra-cellulaires a été étudié chez 50 nourrissons et enfants, par la micro-méthode, dérivée de celle au thiosulfate. L'auteur a mis au point la technique, et a trouvé les résultats les plus valables par des déterminations sur le sang capillaire; il discute ensuite, les limites de la méthode. Il a observé une diminution

rapide du volume des liquides extra-cellulaires, au cours des six premiers mois. La chute atteint 44 à 30 % du poids du corps. Au cours de la seconde enfance, la diminution se poursuit progressivement. Si la diminution est exprimée en litres par mètre carré de surface corporelle, elle est certainement moins accusée, surtout au cours du premier mois.

Das extrazelluläre Flüssigkeitsvolumen bei Säuglingen und Kindern.

Das extrazelluläre Volumen von 50 Kleinkindern und Kindern wurde mit einer Mikromethode der Thiosulfatmethode studiert. Diese Technik wurde zuerst gerufft und man fand, dass die mit Kapillarblut ausgeführten Bestimmungen die zuverlässigsten Resultate gaben, und die Grenzen der Methode werden diskutiert.

In den ersten sechs Lebensmonaten wurde ein rapides Absinken des extrazellulären Volumens beobachtet. Diese Verminderung des Volumens betrug 44 % bis 30 % des Körpergewichtes. Während der Kindheit erfolgt ein weiteres Absinken. Ausgedrückt in Litern per Quadratmeter Körperoberfläche wurde ein weniger ausgesprochenes Absinken beobachtet und dieses hauptsächlich im ersten Lebensmonat.

El volumen liquido extracelular en niños y infantes.

El volumen extracelular de 50 infantes y niños ha sido estudiado por una micro modificacion del metodo del tiosulfato. La tecnica fue primero probada y se encontro que las determinaciones llevadas a cabo en la sangre capilar dan los resultados mas consistentes, y ciertas limitaciones del metodo son discutidas.

Una rapida caida del volumen extracelular se observo durante los primeros 6 meses de vida. La caida era desde 44 % a 30 % del peso del cuerpo. Al expresarla por litros por metro cuadrado de superficie del cuerpo se observaba una caida menos pronunciada y solamente durante el primer mes de vida.

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Chemotherapy in Infantile Diarrhoea

A Trial in 173 Infants

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During the last decade, the treatment of infantile diarrhoea has changed radically with the use of chemotherapeutic agents and a detailed consideration of the water and electrolyte balance of the infant. The introduction of these two therapeutic factors during the same period makes it difficult to judge the value of chemotherapy alone. Infantile diarrhoea is not a single clearly defined disease, and therefore one does not expect that one chemotherapeutic drug would provide a specific cure for all cases.

Periodic reviews of the results of treatment of this condition are necessary in order to judge past methods and to revise accepted routine of therapy. This paper represents an attempt to assess our experiences during a two year period and, on that basis, to consider a revised regime of treatment for the future. It describes a trial of five chemotherapeutic agents (penicillin, sulphadiazine, streptomycin, aureomycin and chloramphenicol) in 173 cases of infantile diarrhoea admitted to this department during the years 1952 and 1953. Several other cases were admitted during this period, but were either withdrawn from the trial for various reasons mentioned below or not included in the trial as their condition on admission was desperate. Where there was immediate danger to life on admission, the infant was excluded from this trial, and aureomycin was prescribed as being the most potent broad-spectrum antibiotic available. Our aim was the assessment of the relative value of these five drugs in aiding recovery from diarrhoea, and survival rates were not considered. During recent years the mortality rate from infantile diarrhoea in this department has been very low.

Clinical Material

Details of the 173 patients are given in Table 1. They were admitted from a large number of places, mostly rural. The nutritional status was

graded into three categories, according to the comparison between the infant's weight on admission and the mean weight for the appropriate age-group of children as presented by PALMER and CIOCCO in their tables adapted from the University of Iowa studies. The status was graded as "Good" where the actual weight was 86 % or over of the mean weight, "Medium" where the actual weight was between 76 % and 85 %, and "Poor" where 75 % and below. No special consideration was given to premature infants, who thus tended to be included in the "Poor" group. Even allowing for dehydration on admission, the striking feature of our cases was that the majority were poorly nourished. The experience during the years 1952 and 1953 therefore corresponds with that of previous years, as described by FRIEDMAN of this department in his report on 289 infants with diarrhoea.

TABLE I

Details of 173 infants grouped according the therapy.

Group		Total	Control	Penicillin 1	Sulphadiazine 2	Streptomycin 3	Chloramphenicol 4	Aureomycin 5
Sex	Male	90	17	13	18	15	11	16
	Female . . .	83	17	15	11	12	14	14
Age	Under 6 months	86	13	14	17	12	14	16
	6 months and over	87	21	14	12	15	11	14
Nutritional state	Good and medium . .	56	9	15	9	6	6	11
	Bad	117	25	13	20	21	19	19
Season of admission	October–March	67	16	9	9	11	11	11
	April–Septemb.	106	18	19	20	16	14	19
Type of case	Severe	79	13	13	15	12	11	15
	Mild	94	21	15	14	15	14	15
Parenteral infections		20	3	3	3	2	3	6
Total number		173	34	28	29	27	25	30

The severity of the individual case of infantile diarrhoea was graded according to the need for special attention to fluid therapy within 48 hours of admission because of the general condition and the state of hydration. Those cases receiving hourly drinks by mouth were graded as "Mild," whereas the need for larger amounts of fluid by either intraven-

or gastric drip classified the case as "Severe". During the latter part of 1953 gastric drip infusions in this department have proved much more effective than subcutaneous infusions, and in many cases of definite dehydration as effective as intravenous fluid therapy.

Of the 13 children over one year of age, only one was over two years. The sex incidence was virtually equal. Each readmission was regarded as a fresh case.

Parenteral Infections

These are noted in Table 2, which includes all infections diagnosed within 36 hours of admission. There was no significant correlation between the presence of a parenteral infection and the severity of the case. Although the group receiving aureomycin showed a larger number of parenteral infections, four of the six infections were noted in "Mild" cases.

TABLE 2

Details of 173 infants grouped according to duration of diarrhoea.

Group		No. of cases	Day of treatment on which diarrhoea ceased			Transfer cases
			0–3	4–6	7 and over	
Total		173	25	67	29	52
Age	Under 6 months	86	12	32	14	28
	6 months and over	87	13	35	15	24
Nutritional state	Good and medium	56	9	23	9	15
	Bad	117	16	44	20	37
Season of admission	October–March	67	10	33	9	15
	April–September	106	15	34	20	37
Type of case	Severe	79	9	27	13	30
	Mild	94	16	40	16	22
Parenteral infections		20	4	5	4	7

Routine Treatment

This followed the general lines described by FRIEDMAN. For the first 12 to 24 hours after admission, the patient was kept on clear fluids either by mouth, intravenous drip or gastric drip, with the selective addition of sodium lactate and potassium salts. Blood and plasma were often used. Small frequent feeds of half-cream milk were then commenced, and the quantity of milk was gradually increased according to the infant's progress. Breast milk was not used.

Trial of Chemotherapeutic Agents

Within 24 hours of admission, a patient with infantile diarrhoea was listed on a special roster, so that each consecutive admissions represented a cycle. In accordance with the position on the roster, the infant was then prescribed either no drug (control group) or one of the five drugs under trial. The daily dosage of these drugs was as follows—penicillin by injection 200,000 units, sulphadiazine 0.2 g per kg for the first day and afterwards 0.1 g per kg, streptomycin by mouth 0.125 g four times daily, aureomycin 50 mg per kg, chloramphenicol 50 mg per kg.

Since infants in a desperate condition on admission were not included, this trial did not deal with all the most serious cases of infantile diarrhoea admitted to this department. Cases entered in the trial on admission were withdrawn if bacillary (Shigella) dysentery, salmonellosis or lambliasis was confirmed as a cause of the diarrhoea, if significant diarrhoea was absent on the first day of admission or if a second drug was added during the first 48 hours because of a marked increase in the severity of the diarrhoea or because of other reasons including thrombophlebitis.

Two children who died are not included in this series. One of these two infants died of bilateral adrenal hemorrhage on the day after admission; the other infant died five days after admission, the autopsy showing a markedly fatty liver and pancreatic changes.

The above factors were the cause of the ultimate inequality of the number of infants in each group. Moreover, of those infants remaining in the trial, the control and penicillin groups tended to include fewer of the more severe cases, since these were often transferred to other drugs within the first 48 hours if the diarrhoea did not improve. Stool cultures were performed on every case, but very few infants showed the presence of pathogenic coliform bacilli. Side-effects of the five drugs were insignificant in number or severity.

From Table 1 it will be seen that the six groups are similar in terms of sex, nutritional status, season of admission, type of case and to a lesser degree, parenteral infections. The clinical material in each group therefore permits comparison of the results of therapy.

The Results

The evaluation of therapy in infantile diarrhoea presents many difficulties. The total period of hospitalisation under our local conditions is dependent on external factors, including the current pressure on bed-space and the prompt attendance of parents on receiving notification that

the child may return home. The period of time necessary before returning to a normal diet is usually arbitrary, depending on the physician's routine. Since so many of the inpatients in this department are malnourished, there is a tendency to maintain them during convalescence on concentrated high-protein and high-caloric feeds (20 % half-cream milk) for appreciable periods before proceeding to full milk feeds prior to discharge. The rate of weight gain during treatment is influenced only indirectly by a drug affecting the diarrhoea, since weight changes are the result of several factors including the degree of initial dehydration and the quantity and type of feeds. It is difficult to assess relapses of diarrhoea where strict barrier nursing is not achieved.

These factors therefore led to the use in this survey of the improvement in the number and form of the stools alone as the index of the response to treatment. This, in turn, being recorded by the nursing staff, depended on the individual efficiency of the nurses and on the pressure of work enabling them to change the infants regularly. Bar-Chay and Abelof recorded the end of diarrhoea as from the appearance of a single normal stool, but this is dependent on the accuracy of one observation by a single nurse. On the other hand, the criterion of Lowdon and McNeill that the first of at least three consecutive days of normal stools marks the end of diarrhoea has in practice proved a standard too rigid for many of the reasonably healthy infants in this department. As the standard in this series, therefore, "termination of the diarrhoea" was regarded as being marked by the first of two consecutive days during which a total of not more than one abnormal stool was passed.

Where the diarrhoea ended within the first three days of specific treatment the response was assessed as "Early," between the fourth and sixth days of therapy, as "Moderate," and on the seventh day or later, as "Late". Where an infant was transferred to another drug after the second day of treatment, but before the diarrhoea had ended, because of the apparent ineffectiveness of the initial therapy, the case was recorded as "Transfer" and the disease was regarded as having failed to respond to the originally prescribed drug.

It has been contended that antibiotics influence the course of infantile diarrhoea only by virtue of therapy of associated parenteral infections. Although the number of associated infections in the aureomycin group is relatively high, as recorded in Table 2, analysis of this factor shows that the comparability of the six treatment groups is not thereby affected.

The comparability of the six treatment groups is not perfect but analysis of the factors causing the lack of strict comparability (see Table 2) shows that they do not affect, in themselves, the "day of treatment on

TABLE 3

Duration of diarrhoea according to therapy in 173 infants

Group	No. of cases	Day of treatment on which diarrhoea ceased			Transfer cases
		0–3	4–6	7 and over	
1. Control	34	4	11	2	17
2. Penicillin	28	1	11	5	11
3. Sulphadiazine	29	9	7	3	10
4. Streptomycin	27	2	14	3	8
5. Chloramphenicol	25	4	11	8	2
6. Aureomycin	30	5	13	8	3
Total	173	25	67	29	52

TABLE 4

Duration of diarrhoea according to therapy in 79 infants (severe cases).

Group	No. of cases	Day of treatment on which diarrhoea ceased			Transfer cases
		0–3	4–6	7 and over	
1. Control	13	0	5	0	8
2. Penicillin	13	1	3	3	6
3. Sulphadiazine	15	3	5	1	6
4. Streptomycin	12	0	4	2	6
5. Chloramphenicol	11	1	3	5	2
6. Aureomycin	15	4	7	2	2
Total	79	9	27	13	30

TABLE 5

Duration of diarrhoea according to therapy in 94 infants (mild cases).

Group	No. of cases	Day of treatment on which diarrhoea ceased			Transfer cases
		0–3	4–6	7 and over	
1. Control	21	4	6	2	9
2. Penicillin	15	0	8	2	5
3. Sulphadiazine	14	6	2	2	4
4. Streptomycin	15	2	10	1	2
5. Chloramphenicol	14	3	8	3	0
6. Aureomycin	15	1	6	6	2
Total	94	16	40	16	22

which diarrhoea ceased." It is therefore permissible to compare the six groups on a statistical basis.

Only a much larger number of cases would have permitted a more detailed analysis. It may be concluded from our material that not one of these five drugs had a clear-cut effect on the course of infantile diarrhoea, as seen in Table 3, and that there was no significant difference between the influence of any two of the drugs. Moreover (see Tables 4 and 5) none of the drugs showed a significant advantage or disadvantage with respect to the cases being mild or severe. The lack of an appreciable difference between the effects of these drugs is an important finding of practical value.

It is quite possible that these results may have only a local and topical value, dealing with cases admitted during 1952 and 1953. Factors possibly different in other seasons and places may include the nutrition of the infants, the types of intestinal bacteria, including special coliform strains, and the sensitivity of bacteria to chemotherapeutic agents.

Summary

A controlled trial of penicillin, sulphadiazine, streptomycin, chloramphenicol and aureomycin was carried out in 173 infants with infantile diarrhoea, the majority of whom were malnourished. None of these drugs had a clear-cut effect on the course of the illness as judged by the duration of the diarrhoea.

La chimiothérapie dans la diarrhée du nourrisson. Un essai sur 173 enfants.

Un essai de traitement de la diarrhée infantile a été réalisé chez 173 enfants, dont la majorité était sous-alimentée. Les drogues utilisées ont été: pénicilline, sulfadiazine, streptomycine, chloramphénicol, et auréomycine. Aucun de ces médicaments n'a eu d'effet net sur l'affection, si l'on considère la durée de la diarrhée.

Chemotherapie bei Säuglingsdiarrhöe. Eine Untersuchung von 173 Säuglingen.

Eine kontrollierte Untersuchung über Penicillin-, Sulfadiazin-, Streptomycin-, Chloramphenicol- und Aureomycinbehandlung bei 173 Kindern mit Säuglingsdiarrhöe wurde durchgeführt. Die Mehrzahl der Kinder war unterernährt. Keines der Medikamente hatten einen klaren Effekt auf den Verlauf der Krankheit, gemessen an der Dauer der Diarrhöe.

Quimioterapia en la diarrea infantil. Prueba en 173 niños.

Una prueba de control con penicilina, sulfadiazina, estreptomicina, cloromicetina y aureomicina fue realizada en 173 niños con diarrea infantil, la mayoría de los cuales estaban mal nutridos. Ninguna de estas drogas tuvo un efecto claro sobre la enfermedad a juzgar por la longitud de la diarrea.

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PROGRESS IN PEDIATRICS

Galactosaemia (Galactose Disease)

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Introduction

Galactosaemia is a rare metabolic disorder characterized by the lowered ability or complete inability of the body to utilize galactose normally. GÖPPERT (1917) seems to have been the first to describe the disease. For a comparatively long period the condition received but slight mention in the literature, but during recent years a number of cases have been reported, especially from the U.S.A., so that by now at least 40 unquestionable cases are on record. Only a few European reports on the disease have been published, and it has never before been reported from Scandinavia.

It is unknown whether or not the disease is hereditary. None of the patients have so far reached reproductive age, but it has been diagnosed, with certainty, in siblings (BELL *et al.*; DONNELL and LANN; TOWNSEND *et al.*), and in some cases it is reported that siblings of the patient with galactosaemia died with symptoms which seem to show that the siblings were also suffering from the disease (HOLZEL; JOHNS; JOHNSON).

So far, the disease has been reported twice as frequently in boys as in girls.

Nomenclature

The designation most frequently applied to the disease under consideration is galactosaemia. As, however, galactose may also occur in the blood in the absence of this particular metabolic disorder, the term galactose disease, as was also suggested by BRAY, would have been more correct.

Owing to the apparent analogy with diabetes mellitus, the name galactosis diabetes has been used, but as nothing is known as to a similar pathogenesis, this term does not seem fortunate.

The term galactosis, which has also been suggested in analogy with, e.g., cystinosis, is an incorrect formation.

Symptoms

The infants seem normal at birth. The birth weight is normal; the average weight at birth calculated for 25 children was 3600 g. None of these children were born prematurely.

Symptoms do not develop until the infants have been given milk for some days. Pronounced and protracted jaundice, which begins when the infants are a few days old, must be emphasized as an early symptom. Medical aid has often been sought because of vomiting and diarrhœa from the neonatal period with ensuing weight loss.

In fully developed, untreated cases of the disease the following symptoms are the most conspicuous: malnutrition, hepatomegaly, cataract and mental deficiency. The first three of these are most frequently mentioned in the reports, whereas the state of mental development is considered only in some of the patients, but in all these mental retardation was noted. In the majority of the children whose eyes were examined, cataract was observed, viz. in 27 out of 31. In three of the children in whom cataract was absent, the diagnosis was made during the first weeks of life. The first lenticular changes seem to be nuclear in nature, but later zonular changes may also occur. Cataract may occur early: LANGEWISCH observed it as early as on the thirteenth day of life.

Splenomegaly has been observed in many cases and considerable ascites is occasionally present. Osteoporosis and fever of unknown cause have been described. The Moro and deep reflexes may be absent.

On the basis of these symptoms a presumptive diagnosis may be made, but it can be established beyond doubt only by the demonstration of the abnormalities in galactose metabolism.

Laboratory Examinations

Of these, urinalysis is the most important. The urine is reducing owing to its content of galactose. That the reducing substance is galactose may be shown by the failure of the sugar to ferment with ordinary yeast, by the formation of the specific osazone, or by paper chromatography. In the presence of violent vomiting, some samples of urine may be sugar-free, for which reason the study of the urine must be repeated if clinical symptoms arouse suspicion of galactosaemia. Only part of the galactose formed by the lactose of the milk can be recovered in the urine.

With the exception of one infant in whom treatment was instituted immediately after birth, albuminuria has been found to be present in all cases examined for this abnormality (TOWNSEND *et al.*).

The excretion of amino acids has been studied in a few patients, all of whom showed a considerable increase (see DARLING and MORTENSEN).

There are no ketone bodies in the urine.

The galactose content of the blood is increased. The amount may be determined by one of the common reduction methods after removal of the glucose by fermentation. The uncertainty to which these methods are subject will be discussed later. After oral or intravenous administration of galactose, the galactose level of the blood shows a marked increase, which persists for several hours. Many authors state that the glucose content of the blood shows a simultaneous steep decrease unassociated with clinical manifestations of hypoglycaemia.

The fructose and glucose tolerance curves are normal, although the latter may become pathological in the presence of advanced cirrhosis.

The serum proteins have been found to be lowered in several cases.

Apart from pathological cephalin flocculation, which has been observed in several cases, the liver-function tests are usually within normal limits.

Differential Diagnosis

The presence of sugar in the urine and the elevated level of blood sugar may easily at first lead to a diagnosis of diabetes mellitus. However, the absence of acidosis and normal glucose tolerance will exclude this possibility, and the demonstration of galactose in the urine will result in the proper diagnosis.

Galactosaemia has previously been interpreted as a special form of glycogen disease (e.g., by MASON and ANDERSEN). The hepatic enlargement alone would be suggestive of v. Gierke's disease. However, the acidosis, the low level of fasting blood sugar and the decreased glucose tolerance in that disease speak against a diagnosis of galactosaemia.

The presence of reducing substances in the urine, albuminuria and amino-aciduria may be suggestive of Fanconi's disease.

In most cases, differentiation will be easy if only the diagnosis of galactosaemia is considered. However, there is one disease from which galactosaemia is difficult, if not impossible, to differentiate, viz. congenital hepatic cirrhosis. In the latter condition galactose may also be present in the urine (cf. Bauer's test), and the galactose tolerance may be abnormal. When milk is removed from the diet, galactose will obviously disappear from the urine, but the general condition of the infant will not improve in congenital cirrhosis, which seems to be of importance in the differential diagnosis. Pathological liver-function tests and a possible de-

creased glucose tolerance will rather be in favour of a diagnosis of congenital cirrhosis. Liver biopsy may reveal changes which may be interpreted as having arisen during intra-uterine life (see DUNSKY).

Pathology

Histopathological studies have been reported only in 10 cases. In these studies, attention was focused particularly on the liver. Fatty degeneration and/or cirrhosis were observed. Fatty degeneration was encountered in all the younger infants, while cirrhosis was present in all the older ones; in several patients both conditions were disclosed. The glycogen content of the liver was within normal limits.

BELL *et al.*, whose studies are the most detailed on record, observed in one case vacuoles distended by fat in the epithelial cells of the proximal renal tubules, and the central nervous system disclosed perivascular and pericellular oedema. Many of the oligodentroglial cells in the subcortical fibre tracts of the cerebrum and cerebellum had swollen and pale nuclei.

Treatment

Once the diagnosis is made, the treatment is simple enough, as it consists only in omitting milk and milk products from the diet and avoiding drugs containing lactose and galactose (e.g. Dosipulvis ferrosi tartratis Pharm. Dan.). Several milk substitutes, such as Nutramigen, which are claimed to contain nutrients in sufficient amounts for infants are commercially available.

Several writers recommend a diet rich in carbohydrates. This must, however, be regarded as superfluous, as the metabolism otherwise returns to normal if only milk is omitted from the food.

It cannot be said how long the patient should be kept on an absolutely milk-free diet. Possibly, the galactose tolerance increases with advancing years, but the greatest care must be exerted, at least as long as growth continues.

If cataract formation persists, surgical measures may become necessary at a later stage.

Prognosis of Results of Treatment

In view of the very poor general condition of the patients and the deaths among their untreated siblings who seem to have suffered from the same disease, galactosaemia is likely to be fatal in most cases which are left untreated.

It is unknown whether or not all cases of untreated galactosaemia will ultimately prove fatal; patients with a mild degree of the disease may be able to survive. Thus, BRAY *et al.* reported of a 7-year-old girl with cataract and a pathological galactose tolerance which was disclosed at a medical examination of the children in a school for the blind. This seemed to show that she was suffering from the disease for which she had never received any treatment.

On the basis of the few known cases on record, it is not possible to say anything as to the immediate death rate in patients who have received adequate treatment. The prognosis for life is also unknown, but in the presence of cirrhotic liver the outlook must be supposed to be rather serious.

The immediate result of the change-over to a milk-free diet is that galactose disappears from blood and urine; the albuminuria ceases, and the liver decreases in size. This response may be observed in the course of a few days. The infant will then begin to gain weight, and the subsequent physical development seems in most cases to be satisfactory.

After some time, the serum proteins will increase, the spinal fluid becomes normal and the osteoporosis disappears.

As far as mental development is concerned the prognosis seems less favourable. Mental deficiency or retardation is seen in some cases, while normal intelligence seems to develop in others.

The cataract may disappear completely. Both to this and the other manifestations it applies that the earlier therapy is initiated the better is the prognosis. In some of the cases reported, cataract persisted unchanged; in one it even seems to have progressed (PITT).

The galactose tolerance may increase with advancing years. From the age of 7 years, MASON and TURNER's patient, who was later followed by TOWNSEND *et al.*, tolerated considerable quantities of milk without excreting galactose in the urine. However, the galactose tolerance continued to be abnormal. Apart from this and a low I.Q., no abnormalities were revealed in this patient. He was under observation until the age of 18 years and is thus the patient with galactosaemia who has been followed for the longest period.

Pathogenesis

In all probability, galactosaemia is a congenital metabolic disorder evidenced by the inability of the liver to utilize galactose. The onset of symptoms depends on dietary intake of galactose, but little is known as to the manner in which galactose is capable of interfering with the func-

tions of the organism to the extent as is seen in infants suffering from the disease.

As the entire quantity of galactose ingested cannot be recovered from the urine, it is likely that the disorder consists in only a partial abolition of galactose metabolism, and that the disease may vary in severity. In this connection, it is interesting to note that STENSTAM found a considerably lowered tolerance to galactose which he was unable to explain in two young healthy women. It is not unlikely that such cases may represent a mild asymptomatic form of galactosaemia.

In normal individuals, only slight amounts of galactose pass via the liver into the circulating blood. On the other hand, patients with galactosaemia on a milk-containing diet will have an abnormally high galactose concentration in blood and tissue fluid. It may be conceived that the high galactose concentration may have a toxic effect on certain tissues similar to that seen in animals with experimentally produced galactose cataract (see below). On the other hand, these animal experiments did not lead to a symptom complex resembling that of human galactosaemia. Thus, it is likely that not only the hypergalactosaemia, but also abnormal processes caused by the special metabolic defect in these children are of importance, principally, perhaps, in the production of renal and hepatic changes. It may be supposed that the liver cirrhosis is secondary to fatty infiltration. According to HIMSWORTH, fatty infiltration which is left untreated will sooner or later be followed by fibrosis. The cause of fatty infiltration of the liver is unknown, but it is reasonable to assume that it may be ascribed to a loss of lipotrophic substances in the urine due to impaired tubular function.

The galactosuria is a consequence of the hypergalactosaemia, since the power of the kidneys to retain galactose is lowered. However, studies by GAMMELTOFT and KJERULF-JENSEN suggest that an active, although slight, resorption of galactose occurs in the renal tubules. In the presence of hypergalactosaemia, this process may strain the tubules to such an extent that the active resorption of other substances is inhibited, explaining the amino-aciduria and perhaps also the hypercalcinuria.

Review of Literature

By reviewing the accessible literature on galactosaemia we have found 40 typical cases in which an unquestionable diagnosis could be made on the basis of the available data (BELL *et al.*, BIRDSONG and WOOD, DAY *et al.*, BRUCK and RAPOPORT, DONNELL and LANN, DU SHANE and HUFFMAN, ELLENBURG and PETERSON, ENNS, FALLS *et al.*, GOLDBLOOM and

Brockman, Goldstein and Ennis, Greenman and Rathbun, Göppert, Holzel *et al.*, Johns, Johnson, Langewisch and Bigler, Maris and Valcke, Mason and Turner, Mellinkoff *et al.*, Norman and Fashena, Patz, Pitt, Reiter and Lasky, Steiner, and Townsend *et al.*).

A number of the cases from the literature which either seem doubtful or on certain points deviate from the typical picture of galactosaemia are discussed below.

Reuss (1908) reported on an infant, aged 4 months, with liver cirrhosis and galactosuria. This report is often quoted as the first known case of galactosaemia. However, on the basis of the available data this diagnosis cannot be made. As Reuss himself also interpreted it, it seems rather to have been a case of primary cirrhosis.

Göppert's case from 1917 must therefore be considered to be the first on record.

Fanconi (1933) described a 9-year-old boy with neurofibromatosis (Recklinghausen), who had previously been admitted to hospital for long periods, but it was not stated whether or not sugar was present in the urine during the hospital stays. The boy suffered from cataract, which was also disclosed in two siblings, but it is not mentioned whether these were suffering from galactosaemia. The boy showed moderate underdevelopment, but normal mental powers. There was no hepatomegaly; the liver function is not mentioned. The patient excreted galactose in the urine, and the galactose tolerance was lowered.

Ussheim's patient (1934) is mentioned by several writers as a case of galactosaemia. The patient, who was 3 months old, excreted slight amounts of sugar in the urine, and the liver was markedly enlarged. He was not placed on a milk-free regimen. Nothing in the case report seems to suggest the presence of galactosaemia.

Only scant data are given in case 1 reported by Bell *et al.* (1950); galactose studies are not mentioned. However, considering that a brother suffered from typical galactosaemia, the data available, particularly the detailed histological report, may presumably be sufficient for a definite diagnosis of galactosaemia.

McCue *et al.* (1951) gave a detailed description of a patient and made a diagnosis of galactosaemia. The patient was a 3-month-old infant who failed to thrive and in whom hepatomegaly, ascites and pathological liver function tests were disclosed. The urine contained albumin and sugar, but the sugar was not identified. Fasting blood sugar was increased and the glucose tolerance markedly reduced. The patient was not examined for cataract. The liver showed cirrhosis and infiltration with fat. On the basis of the data available a diagnosis of galactosaemia cannot be made.

A similar case was reported by EDMONDS *et al.* (1952), who found jaundice, liver cirrhosis and pathological liver-function tests in a 2-month-old infant who failed to gain weight. Galactose and albumin were excreted in the urine. Cataract was absent. Fasting blood sugar was increased, and in a glucose-tolerance test the blood sugar reached 384 mg% after two hours. In addition to cirrhosis, the liver revealed three adenomata with enormous glycogen-infiltrated cells. Absence of cataract in an infant of that age has not been seen in other cases, and pathological glucose tolerance is not encountered in galactosaemia. The case is thus highly atypical. Both this and the one reported by MCCUE *et al.* were possibly cases of primary cirrhosis.

Case 3 reported by BRAY *et al.* (1952) is mentioned by the authors as "a case of probable galactosaemia," but according to the data reported it can scarcely be doubted that it was one of definite, although mild, galactosaemia. A girl, aged 7 years (one of a pair of twins—the other member having died in infancy of unknown cause), had had cataract from early age. Physical growth and mental development were retarded and hepatomegaly was present. The galactose tolerance was abnormal, but the liver-function tests were within normal limits. At the time of the examination, she did not excrete galactose in the urine when being placed on a milk-containing diet (cf. MASON and TURNER's case as followed up by TOWNSEND).

GORTER (1951) saw four children, three of them siblings, with clinical symptoms similar to those of galactosaemia. The cases were atypical with a tendency to bleeding soon after birth, in two of them associated with thrombocytopenia.

DE HAAS (1951, cited by GORTER) mentioned a family in which nine siblings out of ten died within the first few weeks after birth. Galactosuria was demonstrated in four and cataract in one. These children, too, showed a tendency to bleeding. In two cases fatty liver was demonstrated. Only one of the infants was treated, but death occurred at the age of seven days.

Metabolism of Galactose

Our present knowledge of galactose metabolism in man is very limited. The utilization of galactose must be presumed principally to occur in the liver. Various observations suggest that the enzymatic processes in the liver are similar in nature to those active in the utilization of galactose in certain yeast cells, in which a phosphorylation followed by a transformation into glucose phosphate occurs. The details of the metabolic defect in galactosaemia are as yet unknown.

In animal experiments, it has been shown that galactose may exert a toxic action and produce cataract, but it is unknown if the manifestations in patients suffering from galactosaemia are due exclusively to galactose intoxication.

In the literature, it has often been stated that the glucose content of the blood in galactose tolerance tests falls to very low values without the development of concurrent hypoglycaemic reactions. As the methods of analysis are not specific and the technique involved difficult, reports on the observation of extremely low glucose values must be regarded with some scepticism.

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CASE REPORT

Une variété de réticulose à évolution lente

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Médecin-chef: Dr. J. L. Keyzer.

En 1947–1948, j'ai suivi dans ma clinique un enfant, dont le diagnostic a présenté beaucoup de difficultés pour nous.

François A., âgé de 20 mois, dépérissait depuis six semaines à cause d'une maladie apyrétique, évoluant avec une ressemblance frappante avec la coqueluche: quintes fréquentes, *mais sans reprise*. On observe une fréquence accélérée de la respiration (100–120 par minute), et des râles aux poumons, qui sont de nature variable. Le foie est palpable à deux travers de doigt sous le rebord thoracique; la rate est à peine perceptible. Sur le ventre, on aperçoit une vingtaine de papules brunes-rougeâtres de la grosseur d'une tête d'épingle. La radiographie met en évidence un dessin pulmonaire très accentué jusqu'à la périphérie: image quelque peu suspecte de tuberculose miliaire. L'aspect du fond de l'œil est normal, la réaction à la tuberculine est négative.

Examen sanguin: taux d'hémoglobine: 80 %; globules blancs: 12700 (éosinophiles 1 %, formes immatures 1 %, formes à bâtonnets 1 %, formes segmentées 71 %, lymphocytes 15 %, monocytes 8 %); vitesse de sédimentation des globules rouges: 2 mm.

Pendant le séjour à l'hôpital la température dépassa rarement les 37,5 .

Le foie augmenta jusqu'à trois travers de doigt et demi sous le rebord costal.

La radiographie du 2.1 1948 montra de petites ombres annulaires. Dans les poumons on percevait de temps en temps des râles. La dyspnée resta très prononcée jusqu'au paroxysme du 7.1 1948, qui à cause de l'hypersonorité à la percussion fit penser au pneumothorax. Après la ponction, d'ailleurs négative, un emphysème sous-cutané se manifesta (radiographie Fig. 1), qui se propagea à la moitié gauche du thorax pendant quelques jours et qui fut suivi d'une période d'amélioration clinique.

Quelques papules brunes-rougeâtres apparaissent maintenant sur le dos, en même temps que le taux des éosinophiles dans l'hémogramme s'élevait jusqu'à 11 %. Vitesse de sédimentation: 1 mm!

Une nouvelle et dernière période d'aggravation se manifesta du 29.3 1948 jusqu'au 3.4 1948: une dyspnée très marquée (120 à la minute) avec des contractions thoraciques et de nombreuses quintes de toux. De nouveau un grand nombre de papules sombres furent visibles sur la poitrine, le ventre et le dos, partiellement recouvertes d'une croûtelle.

Après cela l'état général s'améliora, le foie devint beaucoup plus petit, bien que

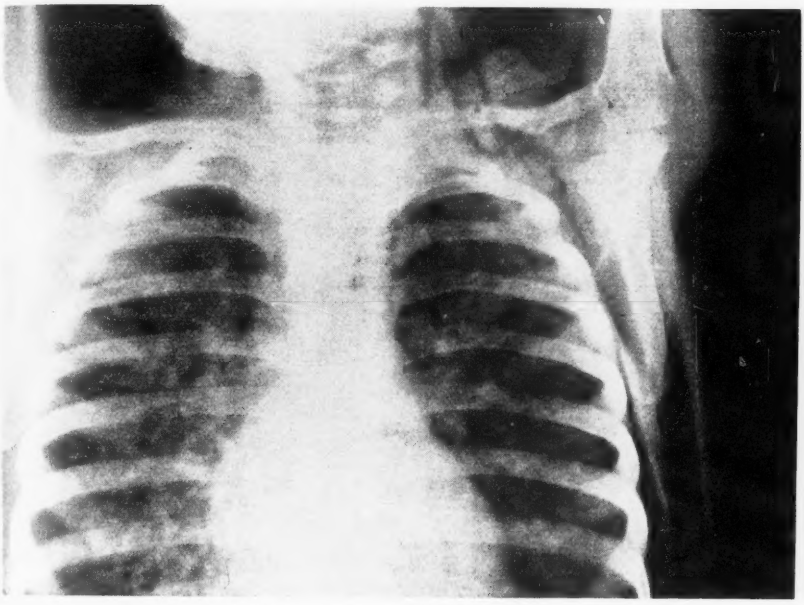

Fig. 1. Emphysème sous-cutané et médiastinal nombreuses ombres annulaires.

la radiographie restât la même et que l'image macroscopique de la peau demeurât inchangée.

Le 28 juin l'enfant quitta l'hôpital avec un diagnostic incertain, car même une biopsie de la peau, pratiquée en février 1948 ne nous avait pas donné une certitude: «Au point de vue microscopique: anomalie épithéliale. Bords: épiderme à gonflement œdémateux. Le fond en est constitué par un infiltrat, qui comporte essentiellement des cellules mononucléaires, dont certaines à grand noyau pâle présentent des nucléoles. L'infiltrat est strictement limité et entoure également les petits vaisseaux plus profonds, les follicules, les glandes séreuses et sudoripares. Il y a peu d'infiltration polynucléaire. L'infiltrat contient assez bien d'éosinophiles, tant mono- que polynucléaires, réunis çà et là en petits amas.»

Le 4.12 1948 l'enfant fut hospitalisé de nouveau, cette fois pour la rougeole, dont le décours était favorable. La dermatose était réduite à de petites érosions sur la poitrine et le ventre. Outre une image tachetée et striée, bien visible comme dans la rougeole on apercevait à la radiographie de *nombreuses petites cavités*.

Le 8.2 1949, hospitalisé pour la troisième fois à cause d'une bronchopneumonie, toujours la même image des poumons: un «emphysème miliaire» fut visible.

Seulement après la lecture de l'article de JULIEN MARIE e. c. j'ai réussi à faire le diagnostic exact.

En 1941 JULIEN MARIE, E. NORMAND, R. MALLET et J. SALET ont décrit l'histoire d'un enfant de huit mois et demi, qui depuis les premières semaines souffrait d'un

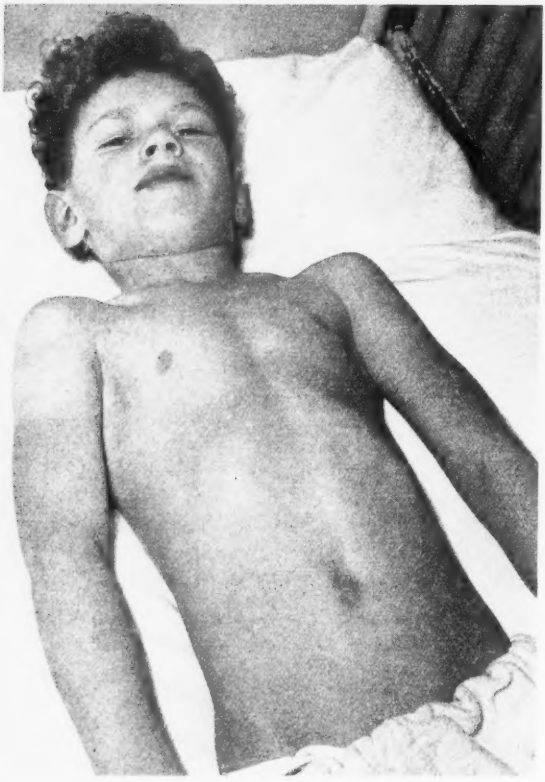

Fig. 2.

syndrôme pulmonaire, caractérisé par une tachypnée très marquée, accompagnée de battement des ailes du nez, de légères contractions, de cyanose et d'une toux coqueluchoïde rare, *mais sans reprise*. A ce syndrôme se joignit une dermatose d'aspect papuleux avec des croutelles brunâtres, qui ne respecta que les extrémités, la face, les fesses et les muqueuses. La température était normale; l'hémogramme montrait une légère leucocytose avec polynucléose. La radiographie des poumons montrait une diminution de la transparence des deux champs pulmonaires. L'enfant décéda quelques semaines après hospitalisation avec une dyspnée extrême, accompagnée d'un emphysème sous-coutané du cou. *L'autopsie* révéla un emphysème médiastinal. A la surface des poumons l'on aperçoit de nombreuses petites bulles emphysémateuses sous-pleurales. L'examen microscopique montre une infiltration de presque tout le poumon, ici confluente, là en petits ilots, ressemblant à des tubercules miliaires. Le tissu infiltré est parsemé de nombreuses cavités de la grosseur d'une tête d'épingle à cette d'un petit pois. La caractéristique essentielle microscopique est un tissu formé de cellules séparées par une très fine trame de substance pulmonaire

élastique. Les cellules présentent un noyau rond ou ovoïde à grains de chromatine, sont riches en cytoplasma et prolifèrent aux dépens des parois alvéolaires. Dans l'histologie de l'éruption cutanée apparaissent des cellules rondes ou polyédriques à chromaphilie nucléaire.

Cette forme de réticulo-endothéliose, qui diffère beaucoup de celles décrites jusqu'ici (pas de fièvre, absence de splénomégalie et d'augmentation de glandes périphériques etc.) fut nommée par J. MARIE et ses collaborateurs «Réticulose cutanée et pulmonaire apyrétique du nourrisson».

Deux autres cas furent décrits plus tard par les mêmes auteurs: chez l'un d'eux l'éruption cutanée manque (9). Le cas de BERNHEIM et FRANÇOIS (1), quoique semblable à celui de MARIE, par les déviations pulmonaires appartient d'après l'indication des auteurs eux-mêmes aux formes aiguës et montre les caractéristiques suivantes: grosse rate, fièvre élevée, affection d'un os du crâne et purpura. L'observation de FONTAN et d'autres (4) rappelle celle de MARIE.

Trois ans après le dernier séjour à l'hôpital nous avons fait revenir notre malade. L'enfant, âgé maintenant de cinq ans, jouit d'une bonne santé, la dermatose laissant comme résidu de nombreuses petites cicatrices blanches (Fig. 2). Il n'existe plus à ce moment d'anomalies radiologiques.

Discussion

En étudiant l'histoire morbide, nous fûmes frappés par la similitude des symtômes de la maladie du petit François avec celles du premier malade de JULIEN MARIE. La tachypnée maximale, qui ne trouvait pas son explication dans des anomalies auscultatives précises, s'aggravant à l'extrême et s'alliant à l'emphysème sous-cutané et interstitiel, était très nette chez notre malade.

La radiographie de 1948 (Fig. 1) montre, outre l'emphysème sous-cutané et médiastinal, l'image de «l'emphysème miliaire» (dénomination de notre radiologiste, le Docteur GOETTSCH), très caractéristique.

La nature de réticulo-endothéliose de la dermatose fut établie maintenant par notre anatomo-pathologiste, le Docteur DEN HARTOG, qui a bien voulu examiner les préparations de la papule cutanée, heureusement conservées (Fig. 3 et 4). Malgré le dommage qu'a subi la croutelle, on voit une infiltration dense et, dans l'image fortement grossie, des cellules réticulaires anormales à noyau hyperchromatique.

L'âge de notre malade correspondait davantage à celui des deux derniers enfants soignés par MARIE. Du reste: pas de fièvre pendant les nombreux mois de son séjour chez nous, sauf toutefois à l'occasion d'une infection accidentelle — le foie seulement temporairement gonflé, pas de splénome-

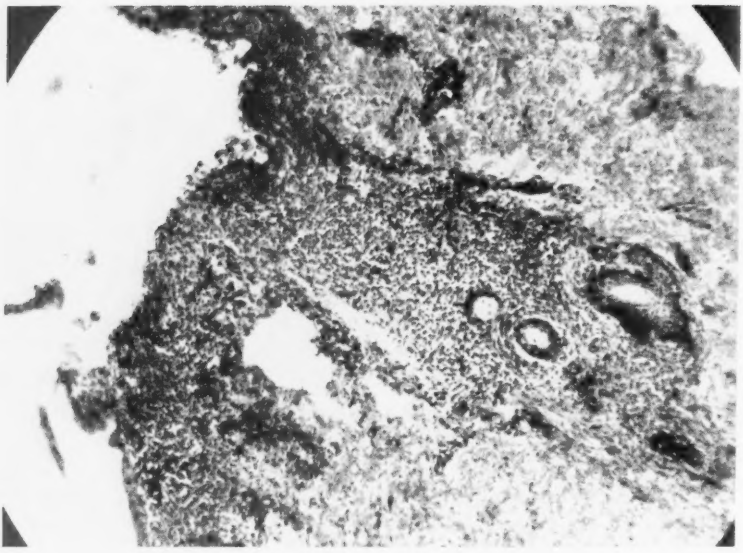

Fig. 3. Peau. Épiderme endommagé. Infiltration dense.

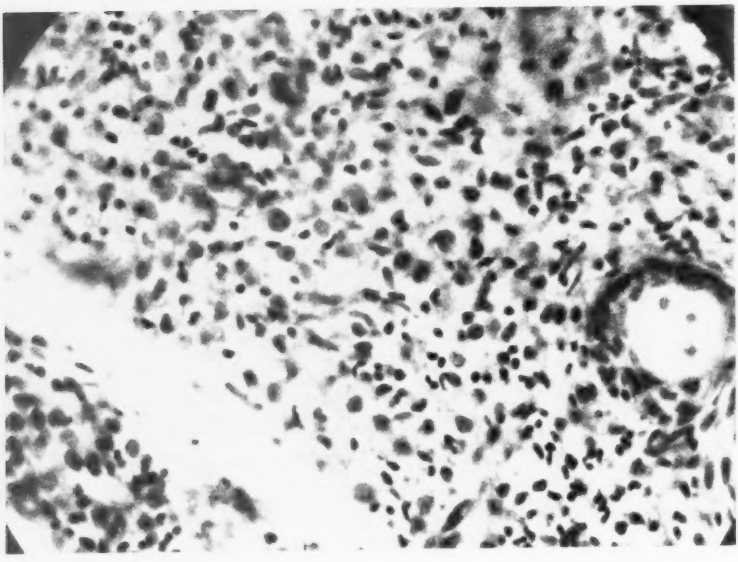

Fig. 4. (Peau. Grossi.) Cellules réticulaires anorm. à noyau hyperchromatique.

galie nette, pas de modification des ganglions lymphatiques, pas de purpura, pas d'anémie, et, malgré une période particulièrement critique avec emphysème sous-cutané et médiastinal, évolution heureuse et guérison complète. Seulement les nombreuses cicatrices sur le tronc font soupçonner ce qui s'est passé.

En ceci notre cas diffère heureusement des trois cas de MARIE, tous à issue mortelle, mais leurs décès ont toujours été précédés d'un stade à évolution lente.

Il n'y a pas lieu ici d'approfondir la question sur l'unité du granulome éosinophile des os, la maladie de Hand-Schüller-Christian et la maladie de Letterer-Siwe, au sujet duquel on a tant publié depuis l'article connu de WALLGREN (12). (Voir les articles récents de ESKELUND et de VESLOT (11). Ailleurs j'ai décrit avec M^elle^ v. d. VELDE un cas, où les difficultés du diagnostic différentiel étaient évidentes (6).

Il faut ici se demander si les cas décrits dans l'observation «princeps» de MARIE et par nous doivent être séparés de la maladie de Letterer-Siwe. On doit reconnaître qu'on n'a pas à faire ici à une «évolution rapide, fébrile, et toujours mortelle», caractéristique de la maladie que nous venons de nommer.

Quant à la littérature sur les réticuloses, on la trouve complète jusqu'à 1946 dans l'excellente monographie de CAZAL (2). CAZAL mentionne outre le cas de MARIE, le cas de pneumo-réticulose de VAN CREVELD, accompagné de pneumothorax, celui de SIWE et celui de GUIZETTI (accompagné d'emphysème médiastinal). Cependant vu la haute fièvre, l'évolution rapide et la généralisation, ces cas appartiennent plutôt à un autre groupe.

Depuis lors les observations de BERNHEIM et FRANÇOIS et de FONTAN ont été décrites. Dans la littérature américaine on trouve bien quelques cas de pneumo-réticulose comme le premier cas de SCHAFER, accompagné d'affections du crâne et dans lequel l'emphysème sous-cutané et médiastinal eut une issue mortelle, celui de FREUD, qui représente un exemple de réticulo-endothéliosis leukémique (5), mais quant au processus décrit par MARIE, je ne l'ai rencontré nulle part, si ce n'est dans la littérature française.

MARIE et ses collaborateurs subdivisent la R. E. du nourrisson en trois groupes, dont les deux premières: 1. la réticulose histiocytaire aiguë maligne leukémiforme (type Cathala-Boulanger) et 2. la réticulose histiocytaire aiguë maligne à localisation osseuse initiale ou prédominante (type Siwe) (e. a. le cas de VAN CREVELD), ont tous une évolution rapide et fatale. Les cas suivis par MARIE et par moi-même, qui ai eu la satisfaction de voir la première guérison complète de cette maladie, semblent justifier la constitution d'un troisième groupe de réticulose histiocytaire, pas tou-

jours «maligne», comme le montre le cas de mon petit malade, mais évoluant toujours de façon «lente» ou «froide» et qui est caractérisé par une éruption de réticulides cutanées au thorax et sur le ventre et par une réticulose bulleuse particulière des poumons.

Résumé

Description d'un cas de la réticulose cutanée et pulmonaire apyrétique de Julien Marie chez un garçon de deux ans, avec guérison complète.

A case of reticulosis with a protracted development of the disease.

Report of a case of reticulosis of the skin and lungs, without fever (Julien Marie) and with complete recovery in a 2-year-old boy.

Eine Variation einer langsam entwickelnden Retikulose.

Beschreibung eines Falles von Retikulose der Haut und Lungen, ohne Fieber (Julien Marie) und mit vollständiger Therapie bei einem 2-jährigen Knaben.

Una variedad de reticulosis a evolución lente.

Descripción de una variedad de reticulosis cutanea y pulmonar apiretica de Julien Marie en un niño de dos años, con curación completa.

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Diaphragmatic Hernia into the Pericardium

by GREGERS THOMSEN, JØRGEN VESTERDAL and CARL C. WINKEL SMITH

From the University Clinic of Pediatrics (Head: P. Plum, M. D.) and the University Clinic of Radiology (Head: P. Flemming Moller, M. D.), Rigshospitalet, Copenhagen

The purpose of this paper is to demonstrate a case of diaphragmatic hernia within the pericardial sac.

Case Report

J. 1146/53. The boy was the only child of healthy parents. The pregnancy was uneventful, and the delivery was uncomplicated. The birth weight was 3,400 g. He was breast-fed, but would not thrive, although his mother had plenty of milk. He was put on formula because of the weight loss, but he still would not thrive and had regurgitations but only rarely real vomiting. The stools were greenish and foul.

He was admitted to a county hospital 5 weeks old on account of weight loss. A radiological examination showed herniation through the diaphragm.

He was transferred to the University Clinic of Pediatrics one week later. On admission here he was pale and undernourished. There was no cyanosis or dyspnoea at rest, but during feeding he got very dyspnoeic, tired and a little cyanotic, and therefore he was given small and frequent feedings. Examination of the chest organs showed that the heart was dislocated to the left, so that the heart sounds were most pronounced in the left axilla. The apex beat could not be located. To the right of the sternum there was some dullness and decreased respiration.

Radiological examination of the thorax showed that the air-filled stomach and part of the intestine were lying in the anterior part of the thorax, going up through a defect in the diaphragm just behind the sternum. The heart was dislocated backwards. The hernia was the size of a large orange, rounded, and sharply demarcated from the surrounding lung tissue. A barium meal examination (Fig. 3) showed that the hernia contents included the antral part of the stomach, a part of the small intestine and the transverse colon. A diaphragmatic hernia through the foramen of Morgagni was diagnosed.

The child was operated upon when 7 weeks old (5 days after admission) through the abdomen, a transrectal incision being used. Through the defect in the diaphragm and into the thorax protruded most of the stomach and the small intestine, the transverse colon, the spleen and the left lobe of the liver. The hernial sac was partially exstirpated, and a part adherent to the left liver lobe was left untouched, and the diaphragm was sutured to the margin of this. The heart was visible through the defect in the diaphragm, while the lungs could not be seen.

Postoperatively he was listless and needed oxygen permanently. He was in a bad condition and would not take bottle feeds.

Radiological examination immediately after operation (Fig. 4) showed an enormous air-filled cavity in the lower two thirds of the anterior part of the thorax. At

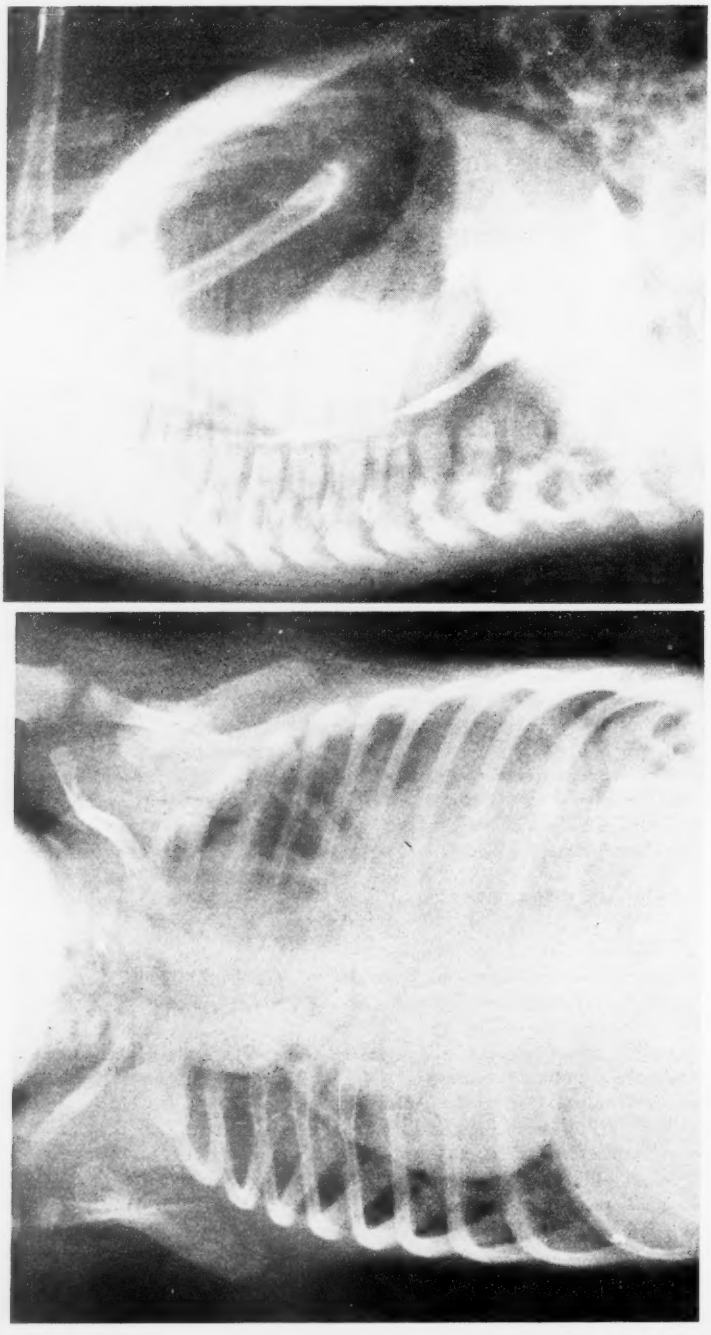

Fig. 1. Upper and lower Aortograms before the first operation. The diaphragmatic hernia contains the stomach and loops of intestine and is sharply demarcated from the surrounding lung tissue.

intestine and is sharply demarcated from the surrounding lung tissue.

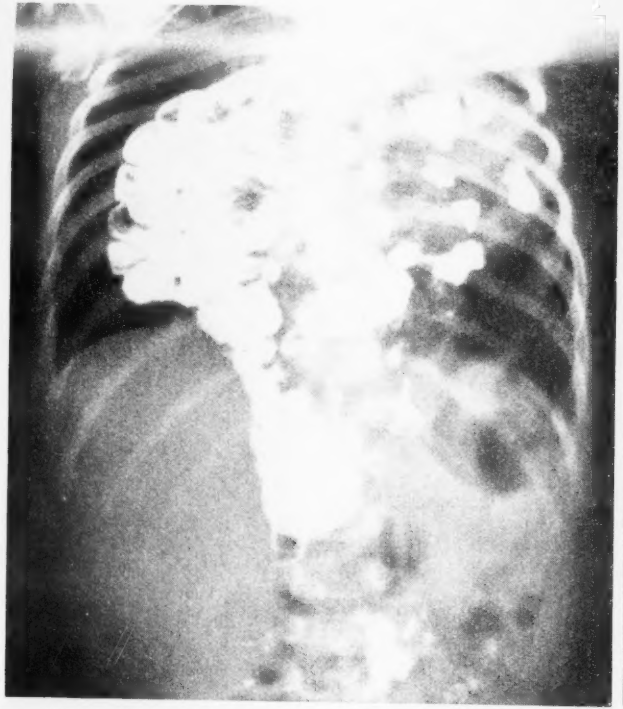

Fig. 3. Barium-filled loops of intestine within the hernia.

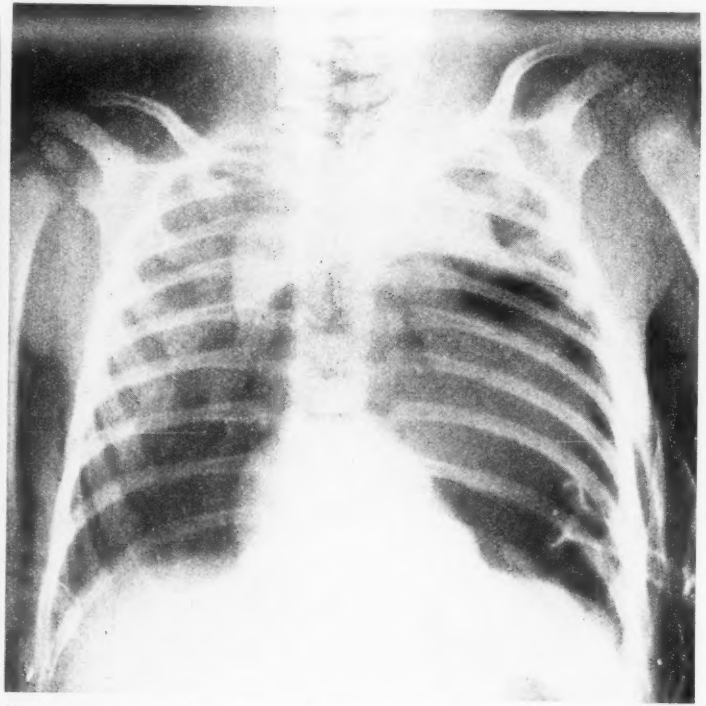

Fig. 4. Appearance immediately after the first operation. Enormous pneumopericardium. At the bottom the left lobe of liver is protruding into the pericardium. The blurred and rather faint heart shadow is seen in the left side of the pericardium.

the anterior part of the bottom of this cavity a rather radiopaque mass as big as a large chestnut was projecting upwards from the diaphragm. The rather faint and blurred heart shadow was seen superposed on the left side of the air-filled cavity. A recurrence of the hernia with protrusion of the stomach into the thorax was diagnosed, but after a barium meal examination had shown that the stomach and the intestine were lying in the abdominal cavity, the air-filled cavity was supposed to be a pneumopericardium. A review of the pictures taken before the operation revealed that the initial hernia had been situated within the pericardium, and this was in accordance with the findings at the operation.

A new radiological examination 3 days after the operation showed that part of the air in the pericardium had disappeared, and the size of the pericardium had decreased a little. The opaque mass projecting upwards from the diaphragm had increased somewhat in size, and the heart shadow was more clearly seen projecting to the left.

Eight days after the operation the air in the pericardium had completely disappeared on the X-ray picture, and the contents of the enlarged pericardium formed a uniformly opaque mass.

His condition improved but slowly, and he still was somewhat dyspnoeic and slightly cyanotic and could not do without oxygen. As an exudate in the pericardium was assumed, a puncture of the pericardium was done a month after the operation and repeated a week later. No fluid was obtained by the first puncture, while 8 ml serous fluid was obtained by the second. This did not alter his condition or the changes in the X-ray picture.

As his improvement was unsatisfactory, a second operation was performed at the age of 3 months, this time by the thoraco-abdominal route on the left side. The pericardial sac was very big and flapping and contained some serous fluid and old blood clots. Moreover, the left lobe of the liver was protruding into the pericardium on the right side of the heart, passing through a large defect in the diaphragm. After reposition of the liver lobe, the defect was sutured carefully.

Postoperatively he did not do well in the first 6 weeks, and radiological examination showed atelectasis of the left lung. By bronchoscopical aspiration 2 weeks after the second operation only small amounts of secretion were found. The atelectasis disappeared gradually, and he improved and gained weight. Sometimes he got a little cyanotic and dyspnoeic. At his discharge from hospital 5 months old his weight was 5,870 g.

A year after the operation he was still doing well, and a radiological examination showed no recurrence of the hernia (Fig. 6).[1]

Comments

Herniation through the diaphragm may occur through the following openings or defects: The oesophageal hiatus, the left or right foramen of Bochdalek, the foramen of Morgagni, and communications caused by congenital absence of the left diaphragm or the central tendon.

These hernias whether congenital or acquired are generally classified

[1] We are indebted to E. Ebbehoj, M. D., Chief Radiologist, Kolding County Hospital, for permission to publish this picture.

Fig. 5. Appearance shortly before the second operation. The enlarged pericardium is seen as a massive shadow.

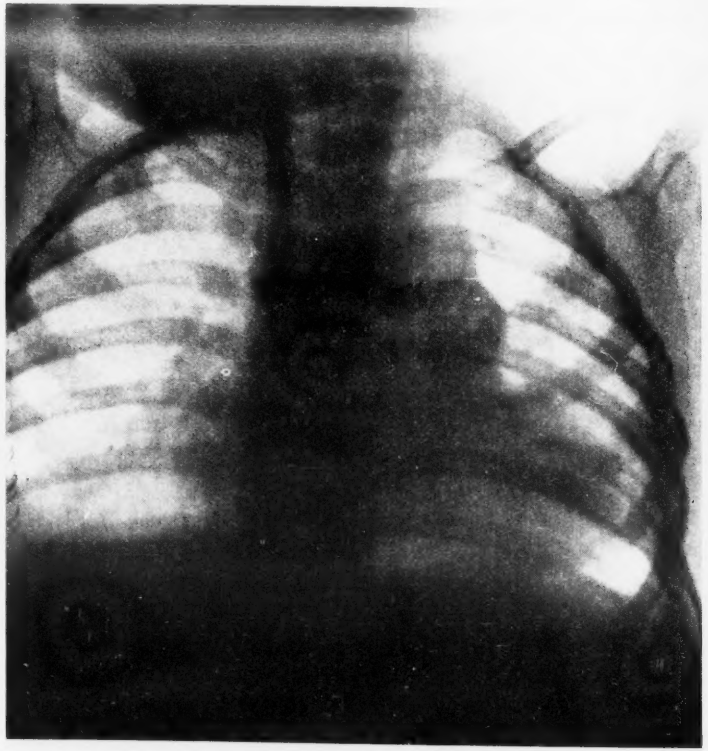

Fig. 6. Radiograph of chest one year after operation.

into true hernias which are surrounded by a peritoneal sac, and false hernias where the hernial sac is not lined with peritoneum or is totally absent.

Diaphragmatic hernia is a rather uncommon disease in infancy and childhood. The various forms occur with different frequency. GREENWALD and STEINER have reviewed the literature from 1912 to 1929, and among 82 cases in children below the age of 10 years they found 29 cases of hernias through the posterior part of the diaphragm (BOCHDALEK), 11 through the oesophageal opening, 7 through the central part, in 6 cases absence of the left diaphragm, and finally 2 cases of herniation through the foramen of Morgagni. In 29 cases the location was not stated. This statement of the relative frequencies of location, however, does not hold true now, as it has been found in later years that herniation through the oesophageal opening is considerably more common than the others.

Herniation through the foramen of Morgagni is very rare, and only 10 cases have been reported where the hernial contents were lying within the pericardial sac, as in our case, which thus is no. 11.

The previous cases have been reported by DECARDENAL et al. (1903), MARTLAND (1909), KEITH (1910) who reported three cases, TAILLENS (1934), O'BRIEN (1939), CASEY and HIDDEN (1944), WILSON et al. (1947), and CRAWSHAW (1952) who reports a case in a Zulu. We should mention that 4 cases have been reported in dogs and one in a donkey (see O'BRIEN). Among the human cases 8 were males, while the sex was not stated in 2 cases. In only one case was a history of trauma given (CRAWSHAW). Four of the cases were children, and all of these were under 3 months of age.

In nearly all the cases the following structures have been found protruding into the pericardium: part of the stomach and the small intestine, the transverse colon, and part of the liver. In our case most of the stomach and of the small intestine, the transverse colon, the left lobe of the liver, and the spleen were lying in the pericardium.

The symptoms have been cyanosis and dyspneoa, especially after feeding, in some cases with relief after vomiting.

The cases of DECARDENAL et al. CRAWSHAW and WILSON et al. were operated upon. In the last mentioned case the hernia recurred after operation. Our case was first operated by the abdominal route. After the operation an enormous pneumopericardium developed and the hernia recurred. A new operation by the thoraco-abdominal route was performed with good result.

Only three of the previous cases were examined radiologically. Neither in these cases nor in ours was the intrapericardial location of the hernia

diagnosed before operation or autopsy. It should, however, be possible to diagnose this condition from the X-ray picture, if the existence of this abnormality is borne in mind.

Summary

An account is given of a 6 weeks old boy with a diaphragmatic hernia through the foramen of Morgagni, lying within the pericardial sac. An operation by the abdominal route was perfomed at the age of 7 weeks. After this an enormous pneumopericardium developed and the hernie recurred. A new operation by the thoraco-abdominal route was performed at the age of 3 months with good result. A review of the previously reported 10 cases is given.

Hernie diphragmatique dans le péricarde.

Les auteurs raportent un cas de hernie diaphragmatique à travers le foramen de Morgagni, reposant dans le sac péricardique, et observé chez un enfant de 6 semaines. Une intervention par voie abdominale a été réalisée à l'âge de 7 semaines. Après celle-ci on notait un énorme pneumopéricarde, et la hernie se reformait. Une nouvelle intervention par voie thoraco-abdominale fut réalisée à l'âge de trois mois, avec un excellent résultat. Les auteurs passent en revue les dix cas rapportés dans la littérature.

Diaphragmahernie mit Durchtritt in das Perikard.

Es wird über einen 6 Wochen alten Knaben berichtet, bei dem eine Diaphragmahernie bestand, die durch das Foramen Morgagni bis in den Perikardsack hindurchgetreten war. Im Alter von 7 Wochen wurde eine Operation durchgeführt, bei der der abdominale Weg gewählt wurde. Danach entwickelte sich ein enormes Pneumoperikard und die Hernie rezidivierte. Im Alter von 3 Monaten wurde erneut operiert und diesmal der thorako-abdominale Weg gewählt. Die Operation war erfolgreich. Es wird eine Übersicht über 10 bisher veröffentlichte Fälle gegeben.

Hernia diafragmatica en el pericardio.

Se relata una hernia diafragmatica en un niño de 6 semanas, que pasaba a traves del foramen de Morgagni, quedando dentro del saco pericardico. Se opero por via abdominal a la edad de 7 semanas. Despues de esto un enorme pneumopericardio se desarrollo y la hernia se reprodujo. Una nueva operacion por via toraco abdominal se realizo a la edad de 3 meses con buen resultado. Una revista de los 10 casos previamente relatados es realizada.

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SUMMARY OF SUPPLEMENT

On Triplets and Quadruplets in Finland

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The purpose of the work has been to investigate Finnish triplets and quadruplets with special reference to the triplet and quadruplet frequency in the country as a whole and in its various regions, hereditary factors, the mother's age and parity, the sex distributions of triplets and quadruplets, the prenatal mortality of triplet and quadruplet infants and their mortality during the first year of life and, finally, the subsequent mental development of the surviving children.

The material comprises all the 633 sets of triplets and 20 sets of quadruplets born in Finland from 1905 to 1952; detailed information, however, is missing on 30 sets of triplets and 2 sets of quadruplets. The *triplet frequency* in Finland during this period was 0.157 ± 0.006 pro mille. If we take into account only the 603 cases to be reported on in detail the frequency was 0.150 ± 0.006 pro mille.

To obtain a clearer idea of the *frequencies of multiple births in Finland* the records have been searched for a longer period, viz. 1881–1952. The averages arrived at are: twins 14.53 ± 0.05 pro mille or 1 : 69; triplets 0.170 ± 0.01 pro mille or 1 : 5929 = 1 : 77^2; quadruplets 0.004 ± 0.001 pro mille or 1 : 274625 = 1 : 65^3. Both twin and triplet frequencies show considerable periodical variations but they have always remained high.

On the basis of the present material no essential difference in triplet frequency is discernible between the various regions of the country. The urban triplet frequency, however, is distinctly lower (0.103 ± 0.013 pro mille) than the rural (0.159 ± 0.007 pro mille). Moreover, all the quadruplets were born in the rural districts, none in the towns.

The majority (some 68 per cent) of the parents of triplets and quadruplets belong to the agricultural population; many of them live in poor social conditions.

Among *unmarried mothers* the triplet frequency is lower (0.101 ± 0.018 pro mille) than among married mothers (0.154 ± 0.006 pro mille).

Heredity seems to play a very important role in the present triplet and quadruplet material: in 75.1 ± 2.3 per cent of the cases of triplets multiples

were born to the parental relatives. Broken down, the figures are: in 35.0 ± 2.5 per cent of the cases to the maternal relatives, in 19.2 ± 2.1 per cent to the paternal relatives, and in 17.0 ± 2.0 per cent to both the paternal and maternal families. In addition in 3.3 ± 0.9 per cent of the cases the siblings of the triplets had multiple births. Moreover, the frequency of recurrent multiple births in triplet families is approx. 10 times as high (19.9 ± 1.7 per cent) as might be expected from the general frequency.

The parental families of the quadruplets also show a high incidence of multiple births, and the quadruplets' families a high incidence of recurrent multiple births, but the figures are so small that no percentages can be quoted.

The *average age* of Finnish *triplet mothers* according to the present material is 33.09 ± 0.03 years, that of all parturients in Finland during the same period only 30.262 ± 0.003 years. Thus the triplets' mothers are considerably older than parturients in general. Most mothers of triplets (30.4 ± 1.9 per cent) are aged 35–39, most parturients in general (27.297 ± 0.022 per cent) 25–29 years. The increasing effect of age on triplet frequency emerges distinctly if the said frequency is determined for the various age groups of mothers. It is lowest (0.033 ± 0.016 pro mille) among women under 20, increasing to its maximum of 0.237 ± 0.027 pro mille at 35–39. — The *average age of quadruplet mothers* is 32.5 years; 72 ± 11 per cent are over 30.

By *parity* the triplet mothers are distributed as follows: 1-para 17.7 ± 1.5 per cent, 2–5-paras 55.6 ± 2.0 per cent, 6–14-paras 26.7 ± 1.8 per cent. Primiparas thus show the lowest rate and 2–5-paras the highest, but a considerable proportion is made up of mothers who have previously had numerous deliveries. A comparison of the primipara : multipara ratio for all parturients and for triplet mothers in 1941–1950 shows that the former include considerably more (35.97 ± 0.05 per cent) primiparas than the latter (22.4 ± 3.5 per cent). As the combined effect of the mother's age and parity, both among triplet mothers and parturients in general, cannot be studied for lack of comparative material it is impossible to decide which of these factors has a greater influence on the rise of triplet frequency with age and parity.

Quadruplets' mothers also, like triplet mothers, are most often 2–5-paras, least often primiparas.

As to the *sex distribution of triplets*, the present material comprises 906 boys and 899 girls, a ratio of 100.8 : 100. For all children born in Finland the boy : girl ratio is 106.4 : 100. On the basis of these ratios the preponderance of boys among triplets would seem to be slightly smaller than it is for all births but the difference is so small that it cannot be co-

sidered of significance. By sex combinations the triplets are distributed as follows: 3 boys 23.5 per cent; 2 boys and 1 girl 26.1 per cent; 2 girls and 1 boy 27.9 per cent and 3 girls 22.5 per cent. 46 per cent of the triplet sets are of the same sex.

The *quadruplet* sets have equal numbers of boys and girls; only 3 sets out of 18 are of the same sex.

No conclusions can be drawn as to the *zygocity of the triplets* and *the quadruplets* as the placenta was examined in only extremely few cases, and in the majority of the sets all or a number of the children have died.

The prenatal mortality of the triplets is 12.60 ± 0.8 per cent and of the quadruplets 17 ± 4 per cent. As the still-birth rate for the whole country during the same period was 2.377 ± 0.007 per cent the intrauterine mortality of triplets is approx. 5 times as high as that of all infants. The rate for quadruplets is somewhat higher still than that for triplets.

All three children were born alive in 75.0 ± 1.8 per cent, at least one child was born alive in 96.4 ± 0.8 per cent, and all the children were still-births in 3.6 ± 0.8 per cent of the sets of triplets. The whole set of quadruplets was born alive in 11 cases out of 18 and was still-born in 1 case.

During the period of 1905–1952 the average *mortality* of the *triplets up to the end of their first year of life* is as follows: during the first 24 hours 19.9 ± 1.0 per cent, during the first 3 weeks of life 36.5 ± 1.2 per cent, and during the first year of life 55.1 ± 1.3 per cent. The mortality during the first 24 hours and the first 3 weeks of life has remained approximately constant throughout the period, but mortality during the first year of life has dropped from 69.9 ± 2.9 to 35.3 ± 5.8 per cent. A comparison of triplet mortality with the general infant mortality in Finland, which has dropped from 12.28 ± 0.03 to 3.36 ± 0.04 per cent, shows that infant mortality during the first year of life has declined more than the corresponding triplet mortality rate. While 3 children were live-births in 77.8 ± 1.7 per cent of the cases in which one individual of the set at least was alive at birth, the complete set was alive at the age of 1 year in only 118 cases, i.e. 20.3 ± 1.7 per cent. In 30 cases one or more of the infants have subsequently died, leaving only 88 complete sets of triplets aged over 1 year now alive in Finland.

As regards the *birth-weights of triplets*, 84.3 ± 1.3 per cent of the infants born in the period of 1931–1952 weighed less than 2500 g at birth and only 15.7 ± 1.3 per cent over 2500 g. The mortality is in inverse proportion to the birth-weight. For infants weighing under 1000 g it is 100 per cent at the age of 1 year, for those weighing 2001–2500 g 22 ± 3 per cent. For all premature triplets the corresponding mortality is 49.6 ± 2.1 per cent and for all full-term triplets 19.0 ± 4 per cent.

The *quadruplet mortality rate* is higher still than the triplet; only 14 out of 60 infants reached the age of 1 year, and only one complete set of quadruplets has survived. All the quadruplet infants weighed less than 2500 g at birth, and all those with a birth-weight of under 1000 g died under 1 year of age.

A total of 6.8 ± 1.2 per cent of the triplets of the present material are *mentally defective*. Idiocy or marked imbecility was encountered in 3.4 ± 0.8 per cent and a less serious retardation of mental development in another 3.4 ± 0.8 per cent of the triplet infants. No definite interrelation is discernible between birth-weight and the mental defect frequency. Nor does the proportion of individuals affected with oligophrenia seem to be higher, at least not essentially higher, among premature than among full-term triplets.

One of the 10 surviving quadruplets is mentally defective. The others seem mentally normal.

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Proceedings of the Danish Pediatric Society

Meeting, April 21, 1954

K. Wilken-Jensen: **Case of allergy to food stuffs (Demonstration).**

Svend Nørregaard: **The care of premature infants as organized in U.S.A.**

As an introduction, the Children's Bureau, which supervises all care of children in U.S.A. and proposes improvements, was mentioned. Thereafter, the organization for care of premature infants in the individual states was explained; this comprises 3 points: ante-natal care, conduct of the premature delivery, and treatment of the premature infant. The first point is not as highly developed as in Denmark; the second involves, among other things, the presence of a pediatrician at these deliveries. The third point commands greatest interest. As a rule, the treatment is concentrated in Premature-Centers which have 3 tasks: treatment of infants, scientific research, and training of physicians and nurses. Finally, an outline was given of how the treatment of premature infants might be organized in Denmark. (To be published in *Ugeskrift for Læger.*)

Discussion: *A. Rothe-Meyer* expressed complete approval of the points of view stated above. Was of the opinion that in the departments for premature infants a sufficient number of special nurses can be trained but that maintenance of the training will be more difficult. Mentioned that special departments are actually capable of reducing the mortality significantly. — *Oluf Andersen* also approved of the proposals and desired extended co-operation between obstetricians and pediatricians. — *P. Brøstrup* desired the institution of centers for treatment of premature infants. — *J. Flamand-Christensen* emphasized the need for pediatricians in departments outside Copenhagen.

Erik Moltke: **Adams-Stokes syndrome as a sequel of acute anemia in a girl aged 8 years.**

(To be published in *Acta pædiatrica.*)

Meeting, June 2, 1954

Holger Buch: **Problems of respiration in newly born infants and their treatment. A review.**

The neonatal mortality has fallen very considerably during the past generation. A more detailed analysis shows that the fall occurred particularly in the age group 1 month to 1 year, while the mortality during the first 24 hours of life has practically not fallen at all and now constitutes more than 1/3 of the total neonatal mortality as opposed to less than 1/10 previously. More than half of the deaths during

the first 24 hours of life are attributable to pulmonary causes. The problems of respiration are therefore questions of primary importance in neonatal physiology and pathology. Respiratory movements are normally initiated by sensitive stimuli and, to a lesser extent, by the chemical changes in the blood due to the separation from the mother. The causes of anoxia may be divided into prenatal, natal and postnatal ones. Paralysis of the respiratory centre due to the exaggerated use of anaesthesia, analgesics and sedatives in the mother, seems to be of greatest significance. Pulmonary emphysema is a more important cause of cyanosis than is atelectasis and, further, the formation of pulmonary hyaline membranes seems to play an increasing role. The guiding principles in the treatment of infants with respiratory problems were dealt with in detail. (To be published in *Ugeskrift for Læger*.)

Discussion: *A. Rothe-Meyer* maintained that good results are frequently observed also without any particular intervention; he asked whether the author was of the opinion that as much activity as possible with the therapeutic measures available was advisable. — *Fr. Neukirch* maintained that the excretion of CO_2 is an important factor in the problems concerning neonatal respiration; he was of the opinion that there must exist considerable retention of CO_2, for which reason attempts should be made to determine this and, possibly, to increase the ventilation and the excretion of CO_2. — *B. Friis Hansen* mentioned a simple apparatus for analysis of oxygen in the inspired air. — *E. Winge Flensborg* warned once more against the treatment of premature infants with oxygen except in emergencies. In such cases, treatment should be of as short duration as possible and with gradual reduction of the oxygen percentage on account of the great risk of retrolental fibroplasia (R.F.). In the Hospital for Children, Martinsvej, Copenhagen, ophthalmic examinations have been undertaken of approximately 220 premature infants with birth weights of 2,000 g since the middle of 1950. These examinations revealed 26 definite cases of R.F., all of them in infants who had received oxygen for 5 days or more, and a definite relationship was demonstrated between the duration of oxygen therapy and the incidence of irreversible R.F. With one exception, R.F. was not demonstrated *during* oxygen therapy but developed frequently just after the cessation of such therapy. R.F. was not demonstrated in 81 premature infants who had not received any oxygen therapy. R.F. was not demonstrated in 42 premature infants who had oxygen for 1–4 days. A more definite relationship was demonstrated between the incidence of R.F. and the duration of oxygen therapy than between R.F. and the birth weight. It must now be considered malpractice to administer oxygen to premature infants except in emergencies, and oxygen therapy must not be continued an hour longer than absolutely necessary. — *H. Dyggve* mentioned the problem of differential diagnosis in cases of intracranial complications, particularly hemorrhages, and drew attention to the significance of prophylactic administration of vitamin K. — *H. Buch* (to *Rothe-Meyer*) did not recommend too much activity but was of the opinion that a certain positive pressure is advisable. — *H. Buch* (to *Flensborg*) agreed that oxygen treatment should be of short duration: low oxygen, preferably for 2 to 3 days only.

Eilif Gregersen: **Vitamin D-resistant tardive rickets. Demonstration of a case.**

The patient was a girl, aged 8 years, with vitamin D-resistant tardive rickets with typical serological, metabolic and radiological manifestations. The case was characterized clinically by dwarfing and greatly deformed lower limbs together with coxa vara and lumbar lordosis. According to American accounts in recent

years, vitamin D-resistant rickets seems to occur much more frequently than previously assumed: the disease, at any rate in U.S.A., was previously to a great extent not recognized. The problems of differential diagnosis and therapy were therefore briefly mentioned. During treatment with massive doses of vitamin D, up to 600,000 units daily, the calcium and phosphorus excretion in the faeces fell by several hundred mg per 2 hours. Simultaneously, the excretion of calcium and phosphorus in the urine increased so that normal conditions were established as regards the total excretion. In the course of 2 months' therapy, the excretion of calcium and phosphorus in the urine thus increased, respectively, from 0.25 per cent to a maximum of 21 per cent and from 43 per cent to a maximum of 66 per cent of the total excretion. The calcium-phosphorus balance, which was negative on admission, showed a surplus of maximally 450 mg calcium and 636 mg phosphorus per 24 hours during treatment. Only partial serological healing has been achieved as yet, as the alkaline phosphatase, possibly on account of the relatively low initial level (approximately 35 units (Buch)), still seems to be uninfluenced despite the employment of the greatest possible doses of vitamin D. The serum phosphorus, on the other hand, became normal already after treatment for 5 weeks and increased from 2.2 mg % to approximately 4 mg %. After the course of 2-3 months, commencing radiological healing became evident by denser bone structure and smoothing out of the epiphyseal lines. When the rickets has finally healed, the patient must be transferred to an orthopedic hospital for corrective osteotomies.

Discussion: *A. Rothe-Meyer* asked about the prognosis and the future treatment. Would osteomalacia develop later? — *E. Gregersen*: The deformities are permanent and the treatment must continue for a long time with maintenance doses of 1/4 to 1/2 of the therapeutic dose until adult age. — *Sv. Brandt* asked about heredity: in certain muscular diseases, the effect of vitamin E seems to be dependent upon hereditary conditions. — *E. Gregersen*: The condition is hereditary in approximately 50 per cent; it has been encountered in siblings.

Jørgen Kringelbach: **The incidence of surgical diseases of the urinary tract in cases of pyuria.**

A total of 72 patients suffering from pyuria were admitted to the Children's Department in Gentofte during the 3-year period 1951-52-53, constituting 79 admissions, viz. 1.7 per cent of the total number of admissions. Not quite half of the patients were under one year, the remainder from 2 to 9 years. Forty-nine were girls and 23 were boys. Twelve of the boys were less than 2 months old and 6 were over one year. The girls were more evenly distributed: 32 of them were over one year old. Half of the children suffered from relapsing attacks of pyuria. In 16 children, changes in the urinary tract as presumed cause of the relapsing pyuria were demonstrated: the great majority of the changes found were congenital deformities of the urinary tract. Thus, in over 20 per cent of the total number of children admitted on account of pyuria to the Department, and in more than 40 per cent of the children with relapsing pyuria, changes of the urinary tract of surgical interest were demonstrated. Eight of the children were operated upon. (To be published in *Ugeskr. f. for Læger.*)

Discussion: *F. Tudvad*: During the past 3 1/2 years, 40 children suffering from pyuria were admitted to the Children's Hospital, Fuglebakken, Copenhagen. Intravenous urography was undertaken in those cases in which relapsing pyuria had occurred. If intravenous urography did not render a definitely normal picture, pye-

lography was undertaken. In a total of 19 children, indirect pyelography was undertaken and of these 11 were normal while the remainder suffered from congenital anomalies or phenomena of stasis. Direct urography showed normal pictures in all cases with one exception and no surgical intervention was performed on any of the children. It is probably desirable to persuade the surgeons to assume a more active attitude even in cases with slighter changes so that later renal lesions could be avoided.

Aa. Gjersøe: **A fatal case of quinine poisoning.**

A child, aged 2 years, was admitted 1 1/2 hours after the ingestion of 25 sugar-coated Chinacetyl tablets (Medicinalco Ltd.) corresponding to approximately 2 1/2 g acetyl salicylic acid. Despite aspiration, gastric lavage, treatment of shock, intubation and artificial respiration, a very serious clinical picture, corresponding to severe quinine poisoning, developed. The picture was characterized by increasing drowsiness, small clonic fits, cardiac weakness with pronounced fall in blood pressure. Death occurred 7 hours after the ingestion of the tablets. The speaker proposed that sugar coating should be forbidden, at least when drugs are concerned whose employment has no rational basis; in this way, a certain number of similar accidents may probably be avoided.

Discussion: *C. Friderichsen* inquired if HCO_3 determinations were carried out on the blood. Mentioned that children generally tolerate quite large doses of quinine. — *Aa. Gjersøe*: The child died before detailed laboratory investigations could be carried out.

P. W. Brøstrup: **Poisoning by overdosage with stimulants of the nikethamide group.**

Mentioned 6 infants admitted in the course of one year, all of whom had been massively overdosed: calculated for a body weight of 70 kg, 17–45 ml nikethamide and 14 and 43 ml cardiazol had been administered parenterally. Three of the children developed severe fits. The indications for injection were in three cases neonatal asphyxia and in three cases general weakness and poor respiration. It was emphasized that newly born infants may very readily be overdosed with these drugs and that the latter are contraindicated in any case where increased liability to fits may be present. It is questionable whether there are any well-defined indications for their employment in newly born infants at all.

Discussion: *Sr. Brandt*: In EEG., 3.5 ml of a 10 per cent pentazol solution is the maximum dose for the releasing of fits.

It was debated whether in calculating the dosage for children from the adult dosage, weight or surface area should be the determining factor. Probably weight is the more correct factor.

Proceedings of the Pediatric Society of South Sweden

Meeting, Kristianstad, Nov. 8, 1953

S. Extrup: **Endocardial fibroelastosis in a group of siblings.**

One after the other, just after 1 year of age, 2 brothers and 1 sister developed cardiac symptoms which gradually developed into serious decompensation. The brothers died at 2½ and 2 years of age. The sister, who was still alive at the meeting, died later at 3 years of age. Postmortem examination of all 3 revealed similar findings: pronounced cardiac hypertrophy, particularly of the left chamber, yellowish-white hyperplastic endocardium, grayish-white rind-like myocardium and stasis organorum. On microscopic examination the endocardium appeared to be composed of elastic lamellae with interwoven fibrous streaks. The myocardium was also markedly changed with coarse fibro-elastic streaks. Pathologico-anatomic diagnosis: Endocardial fibroelastosis. There is one more child in the family, a 10-month-old boy, who so far has not displayed any symptoms of cardiac disease.

(A more detailed report will be given elsewhere.)

I. Gamstorp: **Periodic familial paralysis.**

The results of an investigation on periodic familial paralysis, carried out in collaboration with the county psychiatrist in Kristianstad, H. Mjönes, are presented. The study concerns 2 families comprising 73 cases. The one family includes 5 generations, the other 6, and the disease can be followed from generation to generation without a break. The age of onset is as a rule under 10 years. No case has led to death or more serious invalidity.

B. Söderberg: **Hypophysial myxedema.**

A 12-year-old girl with relatively pronounced symptoms of myxedema reacted with a typical Addison crisis upon the administration of a thyroid preparation. According to the experience of similar reactions in hypophysectomized individuals Neo-teron was given, and thereafter complete substitutional therapy could be instituted.

(The case is published in more detail in an endocrinologic journal.)

Meeting, Malmö, May 9, 1954.

S.-I. Björklund and C. C. Jensen: **The excretion of steroids in children of diabetic mothers.**

The excretion of 17-ketosteroids in 7 newborn infants of diabetic mothers was compared with the excretion in 16 newborn normal infants. During the first 48 hours the former excreted up to 6 times as much as the latter. During the second week there was a tendency towards the same values as in the normal cases. The excretion of 11-oxysteroids in 8 infants of diabetic mothers was compared with that in 3 newborn normal infants and with values in the literature. Other investigators have found rising values from the first 24 hours. The present authors found very high

values in the examined infants of diabetic mothers during the first 48 hours, which decreased towards the second week. The Porter-Silber reaction and determination of 3- and/or 20-ketosteroids according to Venning, both after a modification of Jensen, were carried out on the urine of a child of a diabetic mother. These values were also higher than the normal values. The values of the excretion of steroids found in infants of diabetic mothers indicate an increased adrenocortical function in those children during the first week of life.

L. Sonesson: **Ichthyosis and allergy.**

Thirty-eight cases of ichthyosis vulgaris in children have been collected from Flensburg Children's Hospital, the Dermatologic Clinic of Malmö and the Department of Pediatrics of Kristianstad Hospital. Of these 38 cases 42 per cent had had infantile eczema; 37 per cent asthma, 29 per cent prurigo Besnier; and 11 per cent hay-fever. Of the cases of ichthyosis who had had infantile eczema, 65 per cent developed bronchial asthma or asthmatic bronchitis. Even in the relatives of the children with ichthyosis a considerably increased frequency of allergic diseases could be demonstrated. The investigation has thus confirmed the previously known condition that ichthyosis predisposes to the occurrence of allergic diseases. The common factor, however, is still to be found; perhaps it lies within the endocrine organs. Another conception is, of course, that the disposition to the different diseases is inherited in a common gene or in mutually connected genes.

I. B. Thurell: **The development of tuberculin sensitivity in BCG-vaccinated infants of tuberculous mothers.**

The development of tuberculin sensitivity has been determined in 63 BCG-vaccinated infants of tuberculous mothers and in 716 infants of nontuberculous mothers. The former were cared for during the first months of life at Flensburg Children's Hospital and were examined with 1 mg of Mantoux, the latter were tested with the Néotuberculine cutaneous test at the municipal Children's Welfare centers. At 2 months of age 16 per cent of the children of tuberculous mothers and 94 per cent of the children of nontuberculous mothers were tuberculin-positive. There are three possible explanations of this difference. The first is that Néotuberculine produces more certain evidence of tuberculin sensitivity in BCG-vaccinated infants than 1 mg of Mantoux. Comparison of the two methods reveals, however, that 94 per cent of the children who are positive with Néotuberculine are also positive with 1 mg of Mantoux and, on the other hand, 85 per cent of those who are positive with 1 mg of Mantoux are also positive with Néotuberculine. The second conceivable explanation is that the tuberculous mother transfers immune-bodies to the fetus, sufficient to prevent a BCG-vaccination from provoking tuberculin allergy during the first months of life. Experiments are in progress to demonstrate these eventual antibodies with Middlebrook Dubos' agglutination reaction, but since the material is limited nothing can be said as yet regarding the results. The third theory is that the nonspecific infections often contracted in the hospital by children of tuberculous mothers should counteract their ability of producing the specific tuberculin allergy. A recording has been made of the tuberculin reactions of 640 hospitalized infants. Of these 37 per cent were tuberculin-positive at 2 months of age. The explanation of the fact that the children of tuberculous mothers become positive so late probably lies in a joint action of immune-bodies from the mother and nonspecific infections in the child during the first months of life.

Per Selander: **Some hospitalization problems from the parental point of view.**

As a result of warnings expressed by different quarters of psychic injuries in children after institutional care some investigations have been carried out to determine the magnitude of these problems. Regarding the proposal of *Spence* that the mothers should, from the very beginning, take care of their newborn (who are placed in the same room as the mother—"rooming-in") an interview with 951 new mothers at the Obstetric Clinic in Malmö revealed that only 11 per cent of them approved of such an arrangement. The desire of having the child in the same room was twice as great in social group I as in social group III. Of 99 mothers who had previously experienced a modified form of rooming-in 90 were opposed to this system. Among the 57 foreign mothers admitted to the clinic the desires were the same. Inquiries have been made among the parents of 472 children who had been admitted to Flensburg Children's Hospital for various reasons, regarding the mental status of the children during the first month after hospitalization. Sixty-four per cent were reported to be in the same mental status as prior to admittance. Eleven per cent were reported to have undergone considerable mental deterioration, whereas twenty-five per cent were reported to be considerably mentally improved. The highest frequency of improvement occurred in the ages between ½ and 5 years. The most common improvement was that the child had become calmer, thereafter he had better appetite and sleep and had become more obedient. — Eleven per cent were reported to have undergone considerable mental deterioration. The highest frequency of psychic trauma, 14 per cent, occurred in the ages 1–5 years; the lowest in the ages 6–15 years. The deterioration lasted for more than 4 weeks in 2 per cent of the cases. The most common deterioration was that the child had become more restless, thereafter more defiant and had disturbances in his sleep. An 8-year-old girl (=0.2 per cent of the children), was reported to have required medical care for the psychic trauma after hospitalization. Of these children 2 again began to wet the bed and 2 again began to bite their nails. Jactations, impaired speech, masturbation and finger-sucking were not observed among those with psychic trauma. In order to determine what part the hospital care *per se* has in these symptoms the same investigation was carried out among the outpatients. Only the age group ½–5 years has been included. Of these children 11 per cent were reported to have undergone deterioration. The frequency is about the same as in the hospitalized children of the same age group. Of the 425 interviewed mothers of the hospitalized children 9 per cent stated that they preferred not to visit their children; the majority, 58 per cent, desired to visit them twice a week; 4 per cent wished to make daily visits; 69 per cent wanted to come at 7 p. m.; 95 per cent wanted to stay ½–1 hour. While 22 per cent could come only once a week, only 31 per cent could come every day.

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BOOK REVIEWS

Carlo Imperato: La Terapia della Nefrosi nel Bambino.

Edizioni Scientifiche Italiano, Napoli, 1954. 244 pages. Price Lire 1500.

Detailed reports on studies made on 12 cases of nephrosis in children with discussion on the pathogenesis, clinical symptoms and different kinds of therapy. The volume gives a comprehensive record of our present knowledge of the disease.

F. J. Bentley, S. Grzybowski and *B. Benjamin:* Tuberculosis in Childhood and Adolescence.

The National Association for the Prevention of Tuberculosis, London, 1954. 259 pages. Price 30 s.

This is an important up-to-date book on tuberculosis in childhood based upon personal experience and adequate knowledge of the experience of other authors. In its planning the book is principally a presentation of our factual knowledge and offers discussions upon various kinds of practical problems. On the whole the conception of childhood tuberculosis corresponds fairly well to that of Scandinavian authors. In the following only a few points are stressed that seem of special interest to the reviewer. It is maintained that if atelectasis ("segmental lesion") has remained for more than 6 months one cannot expect a full restitution of the pulmonary parenchyma (re-expansion). Out of 169 cases with atelectasis 10 had got bronchiectasia of which already 6 had been operated on. It is believed that after routine bronchograms three-fourths of all cases of long-standing atelectasis show bronchiectasis which is generally of the silent type. The authors look upon the surgical treatment of segmental lesions with some reluctance and do not believe that the advanced anatomical picture of the removed parts of the lung is proof that the operation was necessary. Pleurisy is considered to develop as an expression of a local direct spread from the primary focus or via the blood stream. A hyperergic state is not regarded as essential for the development of pleurisy. Of interest is the discussion as to whether it can be regarded as possible to have prevented primary tuberculosis in the 92 children who died from meningitis and miliary tuberculosis. It is maintained that 72 % of the cases could not have been prevented with the methods at present in use. A Scandinavian doctor is surprised that BCG-vaccination is not mentioned in this connection and that the sources of infection in small children are so often detected too late. That it is important to prevent the primary infection especially in small children is shown by the report that about half of the dead children were infected before 2 years of age. A prophylactic chemotherapy of primary infection is believed to be of value and is recommended in order to prevent miliary and meningitis; at what age such a treatment should be made and how long it should continue is not suggested. It is not necessary to treat quiescent cases of primary tuberculosis, but later, in adolescence, supervision is necessary. The conception of the Scandinavian authors regarding the diagnostic value of erythema nodosum is accepted. It is of interest to read that the authors

have not been able to confirm the opinion of Myers about the danger of exogenous superinfections and they are also in this point on the same line as Scandinavian physicians. The book is very well illustrated with a great number of nice roentgen pictures.

S. D. Morrison: Human Milk. Yield, Proximate Principles and Inorganic Constituents.

Commonwealth Agricultural Bureaux, Bucks, 1952. 91 pages. Price 10/6 net.

Everyone interested in the constituents of breast milk and the amounts of breast milk yield under different conditions should have access to this comprehensive little volume that gives an account of our present knowledge.

Gustav von Harnack: Wesen und soziale Bedingtheit frühkindlicher Verhaltungsstörungen.

Bibliotheca Paediatrica. Fasc. 55. S. Karger, Basel, 1953. 88 pages. Price SFr. 10.80.

The author reports the result of a study of 2,400 children in Hamburg examined at the beginning of school. The purpose of the study was to get a conception of the somatic and mental development of the children, especially in regard to the incidence of behaviour troubles during the early years of age. These troubles have been put in relation to disturbing environmental psychogenic factors. The children have been divided into 5 social groups in order to study the distribution of behaviour troubles within different social strata. It turned out that 61 % of all children did show one or more symptoms of mental disorder; among the most common were hyperactivity, thumb sucking, nail biting, sleeping disturbances and anorexia. The author evaluates the degree of severity of the behaviour trouble from the incidence of combinations of other nervous symptoms and arrives at the conclusion that the most serious ones are enuresis, *paror nocturnus* and anxiety states. Thumb sucking and nail biting belong to the more benign troubles. Nervous disturbances are evenly distributed within different social groups but the type of disorder is different in the various social classes. In the higher social classes disturbances of appetite and hyperactivity are more common; in the lower social classes pilfering, retarded speech development and enuresis. The author regards this as due to neglected education. An analysis of the environmental conditions shows that only one quarter of the children live in normal happy homes. Half of these children had, however, nervous symptoms which the author believes to depend upon constitutional factors or harmful environmental factors that are not so evident and are difficult to analyse. The greatest accumulation of nervous symptoms he finds in children of nervous mothers. All nervous disorders studied show a greater accumulation in children with bad milieu conditions—with only one exception, ties, whose incidence seems to be independent of environmental disturbances. The study confirms previously reported experiences by child psychiatrists regarding the sex distribution of different symptoms. Behaviour troubles are generally more frequent in boys, and in these the more agressive nervous disturbances preponderate, whilst the girls show more passive types of nervous troubles. The author warns against regarding behaviour troubles, in an uncritical way, as morbid symptoms and against introducing therapeutic measures as soon as a child shows some deviations in its behaviour. One should not forget that the child is an individual that stands in the middle of its development and that the process of maturity includes

great spontaneous healing and accomodation possibilities. The therapy should be confined to the more serious cases of neurosis. The book deals with many interesting problems and gives many new and enriching viewpoints and can therefore be recommended.

Birgit Kihlblom

Pediatric Clinics of North America: **Symposium on Cardiovascular Diseases.** W. B. Saunders Company, Philadelphia, U.S.A., February 1954.

The new periodical, *Pediatric Clinics of North America*, has devoted its first volume to a symposium on cardiovascular diseases. In the preface Drs. *Potts* and *Gibson* of Chicago emphasize that "just as the conscientious internist schools himself in the complex problems of cardiology, so must the pediatrician and the practitioner who cares for the well or ill child understand the clinical uses of many special skills and techniques."

The first part of the book is written by *Gibson* and gives a survey of what eyes, hands and ears can tell in the diagnoses of heart disease in children. Too little is said about the value of a careful palpation of the precordium in this chapter (e.g., the importance of palpating the carotid artery in valvular aortic stenosis or the parasternal lift in right ventricular hypertrophy).

Edwards presents a brilliant exposition of the pathological anatomy of congenital cardiac disease. *Miller* gives a critical review of the use of ECG, and *Keith* writes about angiocardiography in infants and children. *Miller* points out the excellent angiocardiographic equipment designed by Swedish investigators such as Wegelius and Lind, Gidlund and Kjellberg.

Cardiac catheterization is described by *Ziegler*, who points out its value also in infants. *Du Shane*, and *Gasul* and *Marienfeld* have written two chapters on the clinical diagnoses in acyanotic and cyanotic malformations of the heart. Nearly all types of congenital lesions are briefly described. Anesthesia for cardiac surgery in children is discussed by *McQuiston*. Adequate oxygenation and elimination of carbon dioxide are important as is hypothermia, which has been used for many years in the *Potts* clinic in Chicago. Several authors such as *Potts*, *Clagett* and *DuShane*, and *Fell* and *Forney* present the modern concept of diagnosis and surgery in patent ductus, aortic arch anomalies, coaretation of the aorta and in "blue babies." Cardiac arrhythmias are discussed by *Langendorf* and *Pick*, and cardiac hypertrophy in infancy by *Johnson*.

It is quite typical of the situation in pediatric cardiology of today that nearly the whole volume deals with experiences from cases of congenital heart diseases. Only two small chapters of 25 pages, out of the 279 which form the volume, are concerned with rheumatic heart disease. The diagnosis is discussed by *Cassels*, and the treatment and prevention by *Rammelkamp, Jr.* and *Stolzer*.

The volume is of great value as it gives a survey of pediatric cardiology of today. It is of greater importance for the practitioner for whom the book is also written, than for the specialist in this field. It can be highly recommended.

Edgar Mannheimer